THE CHEMISTRY OF NATURAL PRODUCTS
VOLUME II

P. DE MAYO

MONO- AND SESQUITERPENOIDS

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THE CHEMISTRY OF NATURAL PRODUCTS

K. W. BENTLEY, *Editor*

Volume I

THE ALKALOIDS

By K. W. Bentley

Volume II

MONO- AND SESQUITERPENOIDS

By P. de Mayo

Volume III

THE HIGHER TERPENOIDS

By P. de Mayo

Additional volumes in preparation

THE CHEMISTRY OF NATURAL PRODUCTS
A series of texts on the constitution of natural products

K. W. BENTLEY, *Editor*

VOLUME II

MONO- AND SESQUITERPENOIDS

P. de Mayo

Imperial College of Science and Technology
London, England

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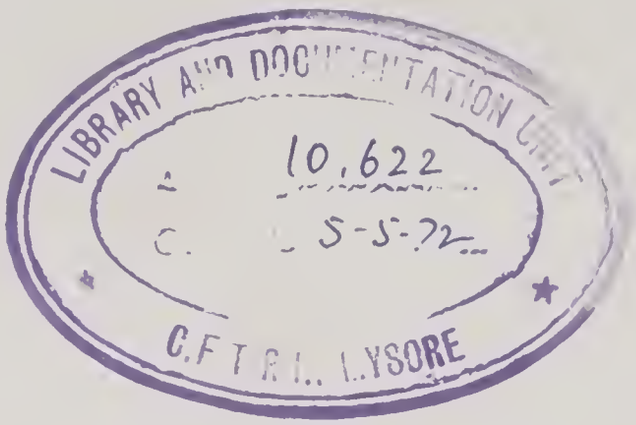

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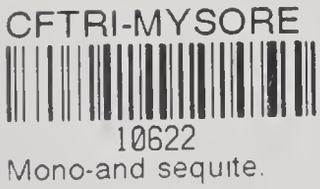

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PREFACE

"Hallo, Rabbit," Pooh said, "is that you?"
"Let's pretend it isn't," said Rabbit, "and see what happens."
—A. A. MILNE

The terpenoids are amongst the oldest studied of natural products, and have, therefore, long held a place in degree courses. When subjected to the study of these compounds the student, the author feels, has a tendency to divide terpenoids into two classes: the dull, but venerable, monoterpenoids and the *parvenu* triterpenoids, the latter being really too complex and bizarre to be of interest to any but the specialist. The rest is silence, with the exception, perhaps, of an occasional murmur about the unfairness of Hm. Wagner and Meerwein. This is a pity because the terpenoids are also very exciting.

Probably the most distinctive feature of terpenoid compounds is the prodigious facility with which they undergo cyclisation and rearrangement, and it is just this which has added the difficulty and interest to their study. Some of the structural contortions undergone by, say, the triterpenoids, are such that a very few years ago they would have been considered incredible. Even with the simpler monoterpenoids the older workers found that during their study the substance investigated had promptly changed into something else, and only by assuming that it *had* changed could progress be made. The manner by which the change was brought about was not studied until much later, and indeed is still being so. The spinal rearrangement of friedelin, the many cyclisations of caryophyllene, and the acid-, base-, and light-induced transformations of santonin are gymnastic processes of an interest comparable to any in organic chemistry.

But stimulation is not all that may be garnered from a study of the terpenoids. Aside from a clearer concept of the versatility of carbonium ion rearrangements, it will be found that these substances represent a useful framework upon which very many general chemical reactions may be studied. These include, apart from synthetic and degradative processes, examples of the stereochemical requirements of reactions and of the relationship of stereochem-

istry and stability and other physical properties. In a sense, correctly studied, terpenoids present almost a microcosm of organic chemistry. In the present work the mono- and sesquiterpenoids have been covered, the higher terpenoids being reserved for the next volume in this series.

No study of the terpenoids could be written which was not greatly indebted to the many volumes of Simonsen's *The Terpenes*, Guenther's *The Essential Oils*, and Gildemeister's *Die aetherischen Öle*. In addition, the author would like to thank Dr. W. C. J. Ross for a view of volumes IV and V of *The Terpenes* prior to publication. He is indebted to his many colleagues, including, Drs. A. S. Kende, S. K. Pradhan, A. I. Scott, M. Shafiq, and J. K. Sutherland for helpful and often pointed criticism, and especially to Drs. G. Morrison and C. J. W. Brooks for reading the entire manuscript.

A particular debt of gratitude is due to Professor D. H. R. Barton, F.R.S., for an inexhaustible supply of keen and constructive criticism in the reading of the whole manuscript, and for devoting much time and enthusiasm to the discussion of its many problems.

Glasgow, Scotland PAUL DE MAYO
April, 1957

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INTRODUCTION

It is probable that from the beginning of his history, man has been interested in the diverse and fragrant odours associated with certain plants. From such a time, then, he may be said to have taken an interest in terpenoid chemistry.

Throughout its earliest development, the study of terpenoids has been associated with that of the essential oils. The development of methods for the isolation of these oils, and for their application, was followed, though much later, by a study of their constituents.

THE ESSENTIAL OILS

Centuries ago it was discovered that the active principles responsible for the odours of plants could be separated from the plant by gentle heating. These principles, as an oil together with an aqueous phase, were collected by condensation on a cool surface. A much later development was the use of steam entrainment. The oils thus isolated became known as "essential oils" or "ethereal oils," the latter designation conveying the subtlety and volatility of the isolate. Recent developments have resulted in a broadening of the term "essential oil" to include materials isolated by the processes of extraction and expression (1).

The production and use of these oils, for the main part for medicinal purposes, began to be of significance only in the sixteenth century, and amongst the substances mentioned at this time are the oils of anise, spike, cinnamon, clove and others. Progress in their manufacture was rapid, and in the *Dispensatorium Valeri Cordi* of 1592 some sixty oils are listed.

For the next two centuries the development and application of these oils remained with the pharmacists. Chemical investigations began only at the beginning of the nineteenth century, probably headed by Dumas. It was then found that in the more volatile fraction of many essential oils there were a number of hydrocarbons, all of the formula $C_{10}H_{16}$. The general term *terpene*, derived from the German *terpentine* (turpentine), was eventually applied to them; it also gradually replaced a number of other words such as *camphene* and *terebene*. Related oxygen-containing compounds were also isolated and the crystalline members became known as *camphors*. Thus there was a "thyme camphor" (thymol) and a "peppermint camphor" (menthol). Again, as the subject developed and expanded, these oxygen-containing compounds were included under the generalised heading of Terpene, the term "camphor" being then restricted to a specific compound. More recently, with the discovery of related substances containing a wide variety of functional groups, the ending "—ene" of terpene, originally signifying hydrocarbon, has seemed inappropriate. There has been a tendency to use the more general term "terpenoid" (analogous to "steroid"), and this will be adopted in the present work.

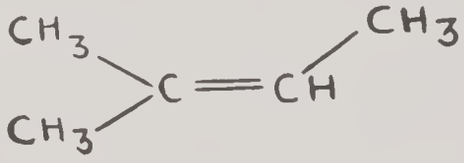
These ten-carbon-containing substances were usually constituents of the lower boiling fractions of the essential oil. When attention was later turned to the higher boiling fractions the presence of fifteen-carbon-containing compounds was revealed. These, the sesquiterpenoids, have since been found to be fairly widespread in nature. Still later work allowed of the recognition of yet other classes of terpenoids, and these are summarised in the following table.

Class	Number of carbon atoms	Sources
Monoterpenoids	10	Essential oils, camphor.
Sesquiterpenoids	15	Essential oils, many bitter principles.
Diterpenoids	20	The rosin from turpentine manufacture, bitter principles.
Triterpenoids	30	Unsaponifiable material from many plants. Saponins, wool fat.
Tetraterpenoids	40	The carotenoids—plant colouring substances.

The last class, although clearly related to the terpenoids, is usually considered with the plant-colouring compounds. In addition, what may be the first pentaterpenoid, an acylic unsaturated alcohol, solanesol (2), has recently been isolated.

It will be noted that the apparent unit or brick from which the terpenoids are built is one of five carbon atoms. This, as regards the simpler terpenoids, was recognized at quite early stages of chemical investigation, and the five-carbon unit was found to be based on isoprene (I). This was particularly striking in the case of the hydrocarbon limonene, which actually gave isoprene on pyrolysis. Isoprene is also obtained from the destructive distillation of rubber, which may be considered, therefore, as a polyterpenoid. This early view of the relationship of isoprene to the terpenoids was a formal one, however, because isoprene itself had not, and still has not, been found in the vegetable and animal kingdoms. It led to a formulation of what has become known as the "Isoprene Rule"; namely, that a terpenoid should be formally divisible into isoprene units. This very general expression has since been modified in certain respects as the structures of more terpenoids have been elucidated. These are discussed elsewhere.

For present purposes the isoprene rule is inexact in two senses, both of which are of comparatively minor significance and frequency. Firstly, some few terpenoids are known, which do not have a number of carbon atoms which is an exact multiple of five. For example, there are a few "monoterpenoids," which contain but nine carbon atoms. It seems very probable that these are in reality derived from ten-carbon terpenoids. Cryptone (II), for instance, is a ketone found in eucalyptus oils. It may be obtained in the laboratory from the hydrocarbon β-phellandrene (III) by oxidation. It is probably of significance, therefore, that β-phellandrene accompanies cryptone in the eucalyptus oil. There are also a number of triterpenoids, which have thirty-one carbon atoms. These are tetracyclic substances closely related to the steroids and the extra carbon atom is contained in the long side-chain. They are, in fact, terpenoid derivatives of the steroid ergostane series.



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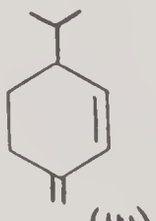

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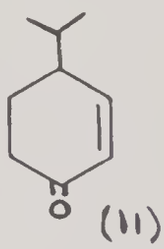


(II)

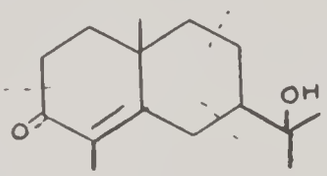
Secondly, terpenoids are known which, whilst having a number of carbon atoms which is a multiple of five, have these arranged in such a way that their structures cannot be divided into isoprene units. Thus, whereas the ketone carissone (IV) is normal, eremophilone (V) is non-isoprenoid. In some cases, at least, it is believed that the isolated non-isoprenoid terpenoid is derived from an isoprenoid precursor.

Whereas the terpenoids have proven to be substances provocative of considerable chemical interest, their industrial application as pure chemicals has been very limited. There are exceptions, notably the sesquiterpenoid lactone santonin which is widely used as an anthelmintic agent. On the other hand, as constituents of mixtures they have achieved considerable technical importance. As components of essential oils they are widely used in the cosmetic and perfumery trade, and related industries. Triterpenoids are constituents of wool fat (lanolin) and also constitute the aglycones of a number of glycosides, such as soap nut saponin, which have the capacity to lower surface tension (wetting agents).

ISOLATION

Since investigations of the terpenoids up to about 1920 were in large part directed to a study of the monoterpenoids, which are mostly liquids, the main technique of separation then developed was fractional distillation. The apparatus then available was of limited efficiency, and in many cases homogeneity was not achieved, though it was much more frequently assumed. For this reason, and because until Tilden's introduction of nitrosite formation (pages 52*ff.*) solid derivatives were difficult to prepare, the same compounds, in varying degrees of purity, became known under several names. The lack of homogeneity, when not recognised, also increased the difficulty of interpretation of their chemical reactions. Recent developments in fractional distillation have greatly increased the power of the technique, and there are now—an important factor—physical techniques for following the processes of purification.

However, more recent work has been concerned with higher terpenoids and possibly the most important single tool employed has



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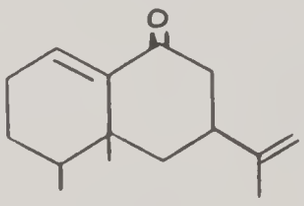


(V)

been that of adsorption chromatography. The use of this technique, usually with alumina or silica as adsorbent, is now standard procedure, particularly with triterpenoids. Smaller amounts than are readily dealt with by distillation techniques can be handled without difficulty—from a few milligrams upwards.

Still newer techniques are those of vapour phase chromatography (3) and partition chromatography (4). Applications of these to terpenoids do not yet abound in the literature, but will certainly rapidly increase, particularly as regards the former. Sub-milligram quantities are easily handled by these processes, and separations of minimal amounts can be achieved, which previously were quite impossible. A further technique which has been applied but little to terpenoid investigation, but which will doubtless be of much use, is that of counter-current distribution (5).

DEGRADATIVE APPROACHES

The classical approach to structural elucidation was, of necessity, brutal. Sufficiently small fragments for recognition had to be isolated. Some processes were moderately specific, in their context, such as hypoiodite oxidation or ozonolysis, whilst others, such as oxidation by potassium permanganate, were not readily controlled. Also, the lack of specificity in reaction entailed the production of several products at each stage for which inadequate techniques for separation were available. The progress made with such limited means was truly remarkable, and is associated with, amongst others, the names of Wallach, Tiemann, and Semmler.

The introduction of the use of dehydrogenating agents to convert cyclic terpenoids to the parent, or related, aromatic systems marked a great step forward. The structural problem was then frequently reduced to the interrelating of functional groups within a known framework.

Recent tendencies are towards the use of milder and more specific reagents or to the use of older reagents, such as chromic acid, under milder conditions. The structural investigations have been very greatly aided by the use of physical methods. These, in particular infra-red and ultra-violet spectrometry, have revolutionised degradative natural product chemistry. In addition, X-ray

studies have begun to solve structural problems directly, and will do so in the future with increased frequency (6). In one case, that of longifolene, the structure has yet to be confirmed chemically. Some of the more important applications to terpenoids of the other physical methods are briefly summarised below.

ULTRA-VIOLET SPECTROSCOPY

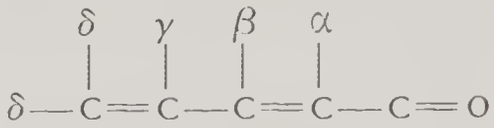
The main use of this technique in terpenoid chemistry is in the detection of conjugation. Empirical rules proposed by Woodward (7) and modified by Fieser (8), are available for predicting the positions of the maxima of the high intensity absorption bands (ca. 7–20,000) of such systems as conjugated dienes and trienes, conjugated ketones, etc. The position of the maximum is dictated by the basic chromophore and by its degree of substitution and, while exceptions may be met with, these rules nevertheless afford a valuable guide. The calculated values are obtained from Table 1 and may be compared with the experimental values given in Tables 2 and 3. There may be a correction if a solvent other than alcohol is used.

TABLE 1

Polyenes

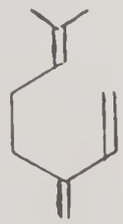
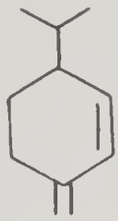
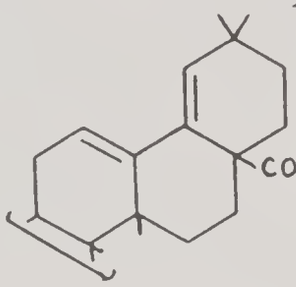
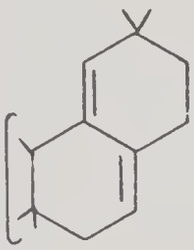
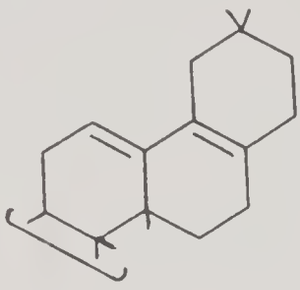
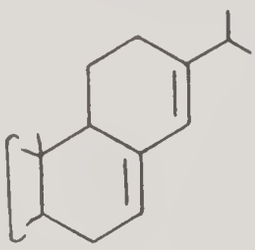
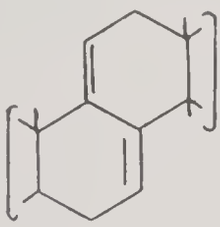
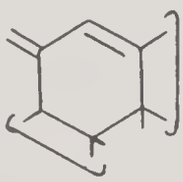
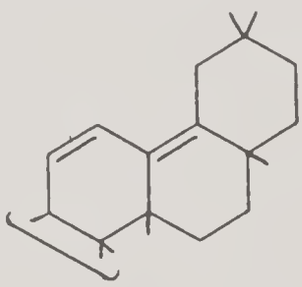
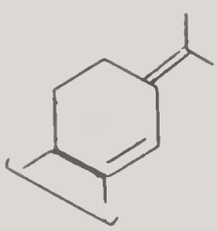
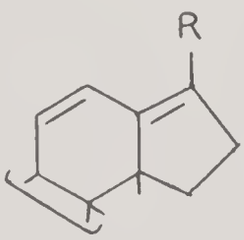
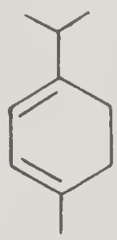
	mμ
Basic chromophore	
Heteroannular diene	214
Homoannular diene	253
For each double bond *extending* conjugation	+ 30
For each C-substituent	+ 5
For each *exo*cyclic C=C in the system	+ 5

Unsaturated ketones



Parent system (one double bond)	215
For each C=C *extending* conjugation	+ 30
For each *exo*cyclic C=C in the system	+ 5
For each C-substituent	
α	+ 10
β	+ 12
γ and δ	+ 18

TABLE 2 DIENES AND POLYENES

CALC. 219  FOUND 225	229  232	244  COOH 232
244  239	244  {236 {243	239  241
244  {236 {243 {251	239  247	244  {242 {250 {260
249  250	R  {246 {255 {264	273  263

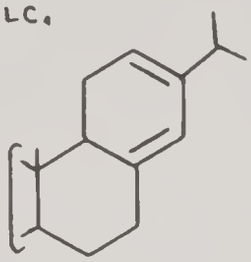
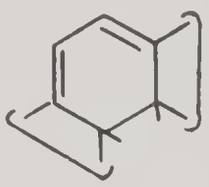
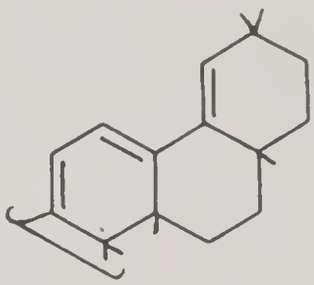
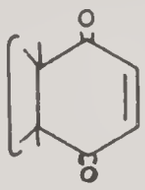
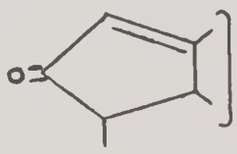
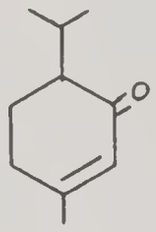
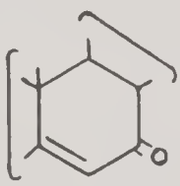
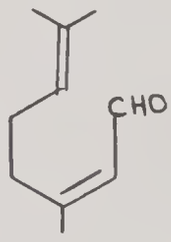
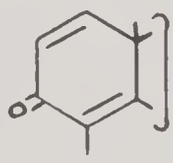
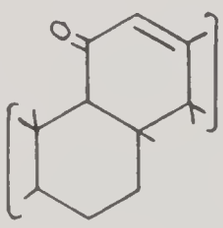
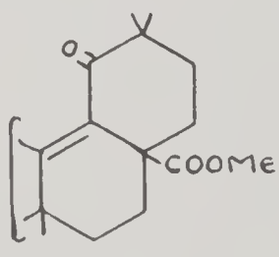
CALC. 278  FOUND 272	283  281	323  310

TABLE 3 CONJUGATED CARBONYL COMPOUNDS

CALC. -  FOUND 221	-  226	239  235
244  237	- 237	-  238
(254)  240	244  249	259  251

Whilst conjugated ketones and conjugated ethylenic linkages absorb in similar regions of the spectrum, they may frequently be distinguished by chemical treatment of the substance with a reducing agent, such as lithium aluminium hydride, and redetermination of the spectrum: the conjugated ethylenic linkages will be in main part unaffected. In addition to the high intensity band ketones and unsaturated ketones also have a further, weak, band at longer wavelength (280–320 mμ; ϵ, ~ 30–150).

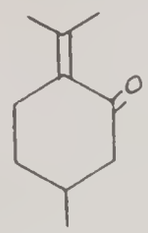
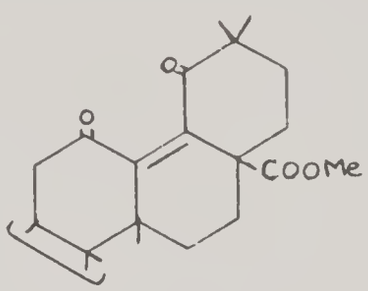
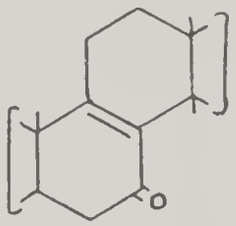
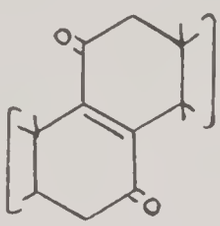
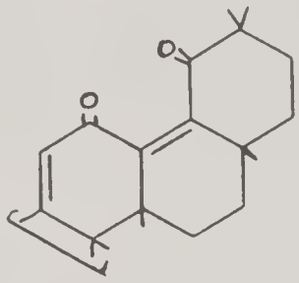
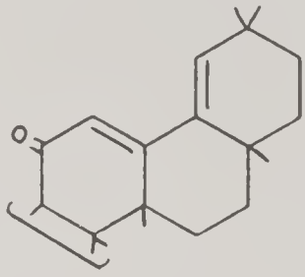
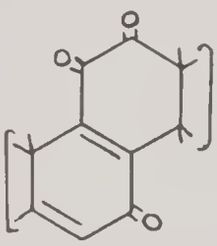
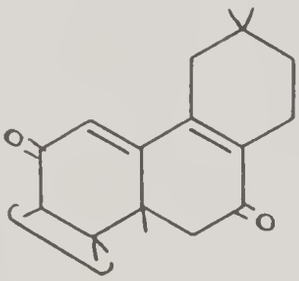
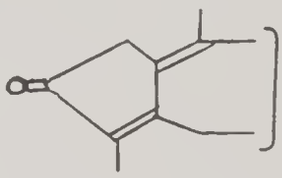
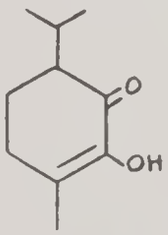
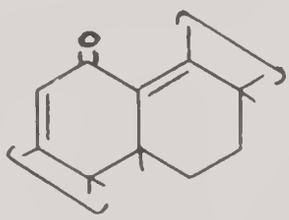
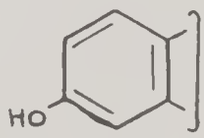
Unsaturated esters, lactones and acids can usually be recognised by their maximum in the 220 mμ region and slow fall-off in intensity. With the normal spectrometer some information can be obtained as to the degree of substitution of a single ethylenic linkage, but it is not very reliable. It should be noted that cross-conjugated systems may have anomalous absorption.

Further applications to terpenoid chemistry, apart from more complex systems of ethylenic linkages and carbonyl groups, include the α- and β-diketone systems. These, together with phenols, have different positions of maxima in neutral and alkaline solution, the latter representing the absorption of the anion. A few common systems are illustrated in Table 3 (9).

INFRA-RED SPECTROSCOPY

The use of this technique is essentially complementary to that of ultra-violet spectroscopy, and its applications cover so wide a range that they cannot be discussed here (10). Of major importance in terpenoid chemistry are two regions of the spectrum. Absorption bands in the first region (ca. 3650–2650 cm^{-1}), apart from carbon-hydrogen stretch, are in terpenoids almost always attributable to O—H stretching vibrations. These, with judicious interpretation, may be used to determine the presence of hydroxyl groups, and related species. Absorption in the second, and more important region (ca. 1820–1640 cm^{-1}), when strong, is usually attributable to C=O stretching. It is possible to recognise saturated and conjugated esters, aldehydes, ketones, acids, lactones, and anhydrides from the frequency of the absorption maximum. Some of the expected positions, in the absence of complicating

TABLE 3 (*continued*)

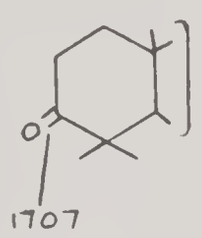
CALC. 254  FOUND 252	–  254	249  255
–  271	–  277	303  284
–  285	–  304	–  305
–  ACID — 274 ALKALI — ~312 (ANION)	–  208 260 295	–  ACID — 280 ALKALI — 300 (ANION)

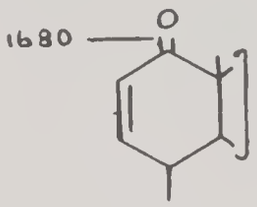
factors (hydrogen bonding, solid state and solvent interactions, etc.) are given in Table 4. These should be compared with specific examples in Table 5.

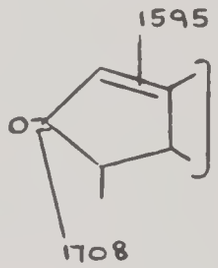
TABLE 4

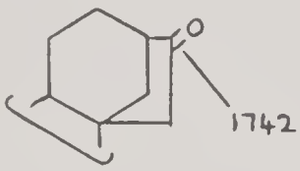
Compound	Region (cm^{-1})	Compound	Region (cm^{-1})
Acids (saturated)	1725–1700	*cyclo*hexanones	1725–1700
Esters	1750–1735	*cyclo*pentanones	1750–1735
Anhydrides-acyclic	1824 and 1748	*cyclo*hexenones	1690–1665
Anhydrides-succinic	1865 and 1782	*cyclo*pentenones	1710–1690
Anhydrides-glutaric	1802 and 1761	α,β-unsaturated-γ-lactones	1760–1740
δ-lactones	1750–1735	aldehydes	1740–1720
γ-lactones	1780–1760		

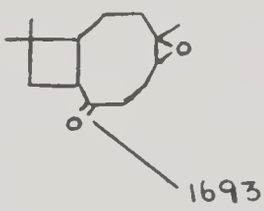
TABLE 5 CARBONYL FUNCTIONS

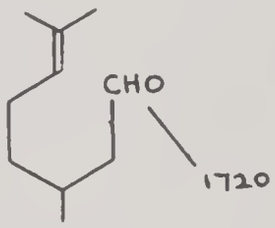


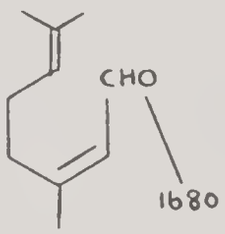


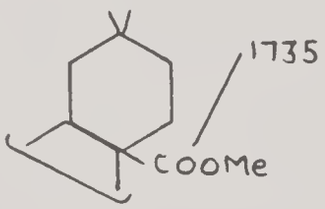


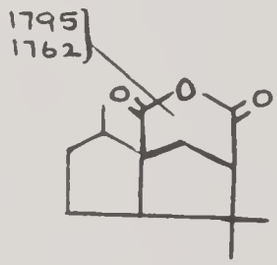


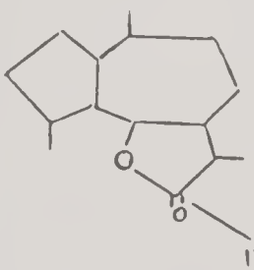


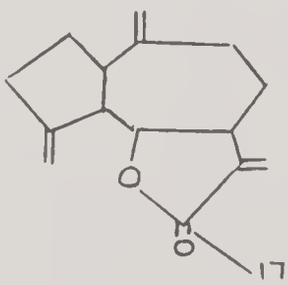


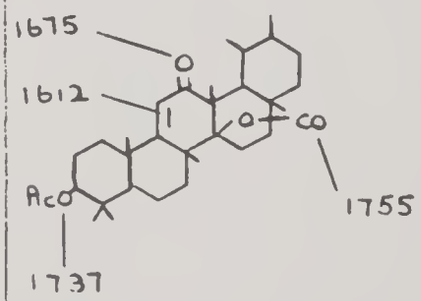




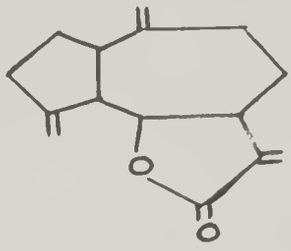








Other important, but less general, applications have been made in other regions of the spectrum. A weak band at about 3050 cm^{-1} has been used as indicative of the presence of a methylene group in a *cyclo*propane ring; a fact which was of use in the elucidation of the structures of such terpenoids as *cyclo*artenol and phyllanthol. A strong band in the 900 cm^{-1} region may be indicative of an *exo* methylene group. The identification of such groupings is always valuable. The case of dehydrocostus lactone (VI) is particularly instructive: all three double bonds could be placed, as no band at 1380 cm^{-1}, characteristic of methyl groups, was present.



(VI)

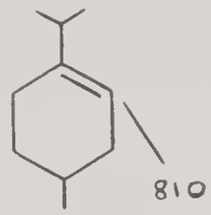
The absorption due to ethylenic bonds substituted in different ways may also be useful, but since these bands are frequently weak, they may be obscured by other bands in substances with complex functional group systems. In Table 6 some instances are given, where bands due to ethylenic and other linkages have been of use.

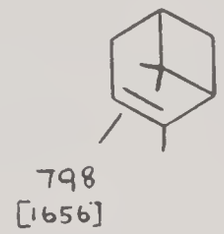
Quantitative infra-red measurements have also been of value in structural investigation, for example, in the determination of the number of methyl groups. Another recent development is the comparison of spectra of deuterated and non-deuterated material. This can be used, for instance, to detect the introduction of deuterium by enolisation (α to carbonyl) by the action of DBr. It has been used to locate the position of *cyclo*propane rings by ring opening with DCl and ascertaining the position of the introduced deuterium. Such applications will be referred to in the subsequent text.

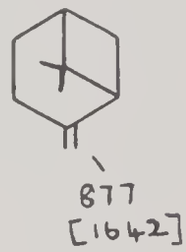
MOLECULAR ROTATIONS

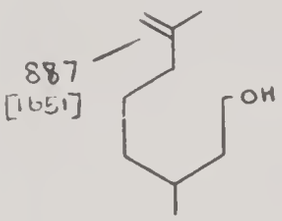
Whilst the determination of the rotations of optically active compounds has been practised, if not consistently, for very many years, it is only within the last ten years or so that it has been realised that such values are a source of much information. Its original purpose was largely the recording of another useful physical constant. In 1936, however, Callow and Young observed that all naturally occurring steroidal alcohols having a double bond at the

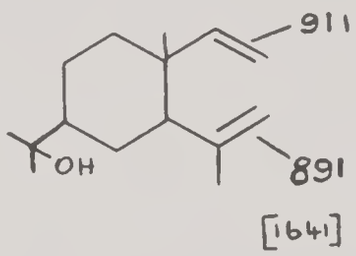
TABLE 6 ETHYLENIC FUNCTIONS

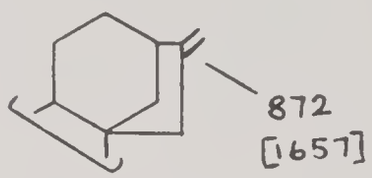


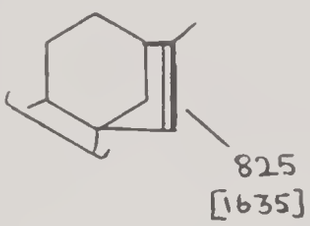


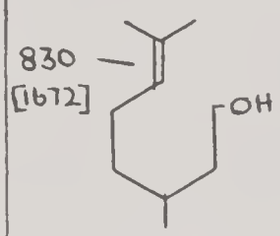


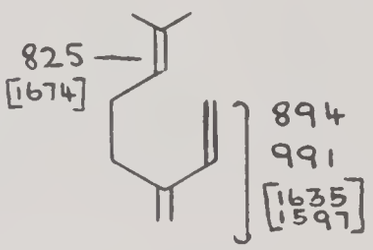


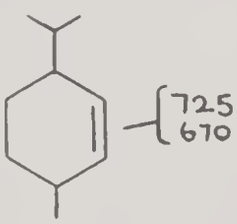


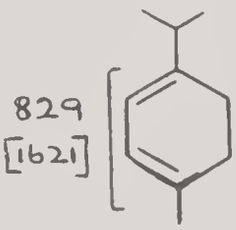


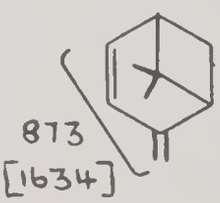












5:6 position are laevorotatory. They also noted that a 4:5 double bond increased dextrorotation (as in VII), whereas a 5:6 double bond increased laevorotation (as in VIII). The applications of the method were further extended by Wallis and his collaborators, and finally Barton (11) developed a method by which rotation became an important tool in the elucidation of the structures of steroids. Later the method was applied to triterpenoids, and, by Klyne (12) and others, to terpenoids in general. The basis of the method is the fact that, in general, *like functional groups in like surroundings make like contributions to the optical rotation.*

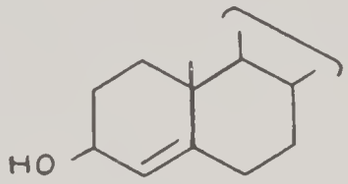
For comparison, rotations are determined, preferably in chloroform solution, and the molecular rotation, $[M]_D$, derived as follows:

$$[M]_D = \frac{[\alpha]_D \times \text{mol. wt.}}{100}$$

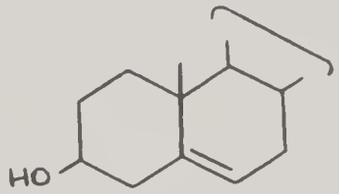
The experimental error expected is of the order of ±2%. As an example, in the table below the changes in $[M]_D$ on acetylation of various common triterpenoids are recorded. It will be noted that these changes are of closely comparable order and of the same sign. These values are different, for instance, from those of some typical steroids, also included for comparison, and the difference is

Compound	$[M]_D$, alcohol	$[M]_D$, acetate	Δ_1 (=Ac − alc.)
α-Amyrin	+ 358	+ 370	+ 12
Ursolic acid	+ 319	+ 319	± 0
β-Amyrin	+ 379	+ 384	+ 5
Oleanolic acid	+ 356	+ 359	+ 3
Cholestanol	+ 93	+ 60	− 33
Ergostanol	+ 64	+ 27	− 37
Stigmastanol	+ 100	+ 69	− 31

attributed to the presence of the *gem*dimethyl group at C_4 in the triterpenoids. A simple and direct application of this is the recognition by Barton (14) of the triterpenoid nature of *cyclo*artenol ("arto-



(VII)



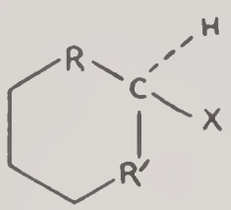
(VIII)

stenone") previously believed to be a steroid. The above facts have been generalised by Klyne and Stokes (13), into a general principle for predicting the signs of rotation of an alcohol, acetate, or benzoate in a *cyclo*hexane ring, provided it is not adjacent to a *cis* fusion to another ring. If the system is represented by (IX) it may also be represented by (X) where the hydrogen atom is presumed behind the plane of the paper.* Provided both R and R′ are not $-CH_2-\overset{|}{\underset{|}{C}}-$, the sign of rotation may be predicted. Extensions of these methods have enabled the prediction of configuration in many terpenoids. Molecular rotations are also valuable as a guide to the particular stereochemical series of compounds to which a new substance may belong. The first important sign, for instance, that the apparently similar triterpenoids euphol and lanosterol had some radical structural difference came from the study of molecular rotations. The power of the method may be judged by its now automatic use as a guide to the prediction of stereochemistry.

It is impossible to cover all the ramifications of this technique in such a short space, a few illustrative examples only being possible. It is necessary, however, to add a very important qualification. The deductions to be made by the application of this method are only valid provided that there is no special circumstance, such as a proximate functional group, which may exert an effect which is not merely additive. This "vicinal effect" as it has been termed, may well reverse conclusions. The methods of molecular rotation are only reliable in systems wherein the centres to be analysed are insulated from others by several carbon atoms.

One extension of the method is due to Mills (15). His procedure differed from the foregoing in that, instead of comparing the derivatives of saturated compounds, he studied the difference in ro-

*In presenting stereoformulae a broken line represents a bond (α) *below* the plane of the paper, whilst a solid thick line represents a bond (β) *above* the plane of the paper.



(IX)

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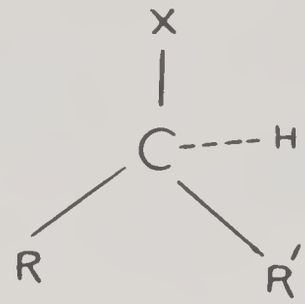


(X)

$R = CH_2\overset{|}{\underset{|}{C}}-$ $\quad R' = -\overset{C}{\underset{C}{\overset{|}{\underset{|}{C}}}}-H$ OR $-\overset{C}{\underset{C}{\overset{|}{\underset{|}{C}}}}-C$ $\quad$ -ve Rotation

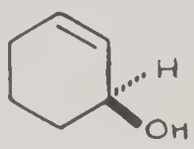
$R' = CH_2\overset{|}{\underset{|}{C}}-$ $\quad R = -\overset{C}{\underset{C}{\overset{|}{\underset{|}{C}}}}-H$ OR $-\overset{C}{\underset{C}{\overset{|}{\underset{|}{C}}}}-C$ $\quad$ +ve Rotation

tation of unsaturated epimeric pairs. A number of pairs were known in the monoterpenoids of which the absolute configuration in space, which is also the configuration in terms of the glyceraldehyde convention (11), was known. All these alcohols were to be considered as derivatives of the optically active (XI) or (XII). An important generalisation could then be made: alcohols derived from (XI) were always much more laevorotatory than the (epimeric) derivatives of (XII). The differences were enhanced by esterification. Another conclusion reached by Mills was that in unsaturated hydrocarbons of the type (XIII) the following held: When the hydrogen atom at the asymmetric centre is two places removed from the double bond in a clockwise direction and oriented above the plane of the ring, then (XIII) will represent a dextrorotatory compound when R, R′ are simple alkyl groups. The value is of the order $[M]_D \sim 150^\circ$ when R′ = alkyl.

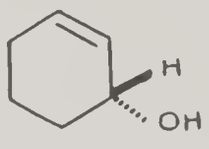
Using these generalisations, the absolute configurations of the sesquiterpenoids lanceol (page 200) and zingiberene (page 194) were deduced.

The above applications of the method have been to single centres. Klyne, extending the technique, has shown that terminal rings as a whole (and, to a lesser extent, non-terminal rings) of a polycyclic system can be treated as a single unit. The principles on which this method was based provide that should the penultimate ring be a saturated unsubstituted *cyclo*hexane ring the contribution of a terminal unit is *very roughly* independent of the rest of the molecule. Some other qualifications are also necessary.

In fact it appears that a large number of chromophores, such as conjugated ketones, for instance, which are associated with large



(XI)



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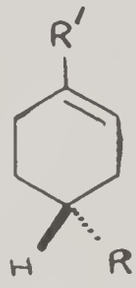


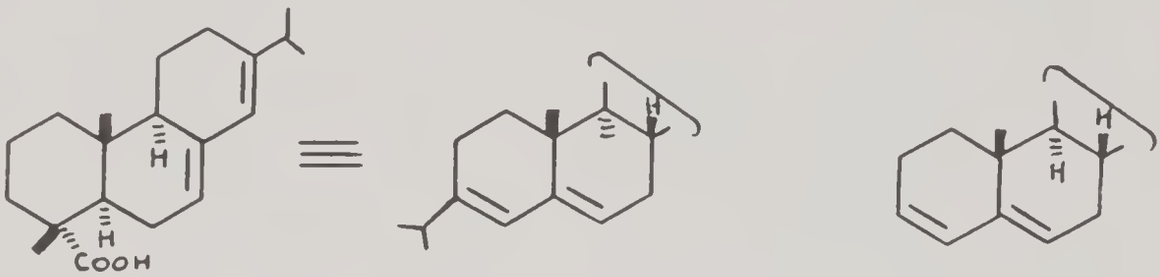
(XIII)

rotations and which are the only such features in a particular molecule, may be used for stereochemical assignment. Amongst the numerous results obtained by the application of molecular rotations was support for the correct stereochemistry of the β-amyrin series of triterpenoids, a correlation of the configuration of triterpenoids with the steroids, and also the similar correlation of some diterpenoids and sesquiterpenoids. Many of the conclusions so reached have been substantiated by other methods. Some of the correlations are shown opposite. In the assignment of absolute configurations, and in other problems, Djerassi and his collaborators (16) have shown that it is important to take a rotatory dispersion curve—that is, the rotation at several wavelengths—rather than relying on the value at the sodium line only. A case in point is that of eremophilone, where the assignation has had to be reversed despite the apparent agreement between the sign and magnitude of the rotation of eremophilone and of the model substance at the sodium D line. The full curves revealed by rotatory dispersion were roughly mirror images crossing near 400 m μ.

NUCLEAR MAGNETIC RESONANCE

The applications of this technique to terpenoids are as yet few. It will undoubtedly become a potent instrument in this field when more machines are available. At the moment, instances of its use in terpenoid chemistry have been limited to proton resonance.

The process depends on the separation and summation of the resonance signals emitted by protons in different (and immediate)

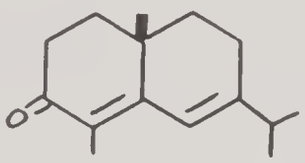


INCREMENT FOR INTRODUCTION OF DIENE SYSTEM

-335°

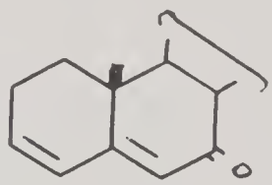
ROTATION OF MODEL

-549°



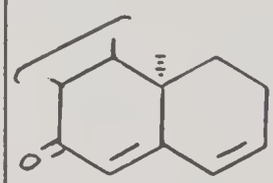
$+745^{\circ}$

TO BE COMPARED WITH :-



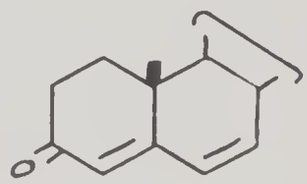
III

-1150°



OR :-

$+410^{\circ}$



environments. The intensities are a measure of the number of sources. One application, for instance, occurs in the chemistry of ψ-santonin. The possibilities (XIV) and (XV) were proposed for an acid. In one case there was a triply substituted double bond—that is, an ethylenic linkage with a hydrogen atom attached—whilst in the other case there was no such feature. Examination of the resonance spectrum revealed that in the region where such hydrogen would be expected to show a peak, there was no signal. Formula (XIV), substantiated by other evidence, was therefore correct. A somewhat similar application was to the structure of eucarvone (page 82). In the more complex case of the sesquiterpenoid helenalin (page 270), the structural elucidation required the quantitative comparison of summed peaks associated with three different environments of hydrogen atoms.

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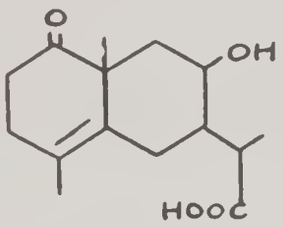
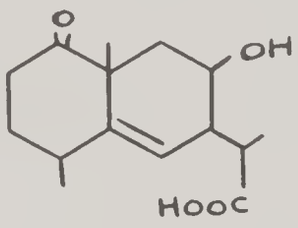


(XIV)



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THE MONOTERPENOIDS

These substances constitute a fairly large family of alcohols, hydrocarbons, ketones, etc., which are important components of the essential oils obtained from the leaves, roots, and bark of various plants. They have pleasant odours, and many are of some industrial importance, though not necessarily as pure chemical individuals.

Because of the difficulty of separation and of characterization, it is not surprising that many of the chemical results obtained by the early investigators were difficult of interpretation. Added to this many of the acyclic members of this group easily underwent cyclisation reactions and certain of the bicyclic members readily rearranged. The latter problem, one of considerable difficulty at that stage of chemical development, required the theoretical genius of such men as Wagner for its solution.

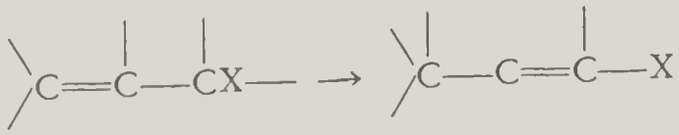
The monoterpenoids may be divided into three classes having zero, one, or two rings; further subdivisions are made on the basis of carbon skeleton.

THE ACYCLIC MONOTERPENOIDS

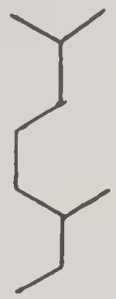
The acyclic monoterpenoids are comparatively few in number, but include some of the most important isolates in perfumery. They were the subject of investigations in Germany (Tiemann, Semmler) and in France (Barbier, Bouveault) from about 1890 onwards. However, these substances, being liquid, were difficult to purify, and many did not give crystalline derivatives (e.g., linaloöl). Others,

whilst giving derivatives, could not be regenerated in a pure condition from them.

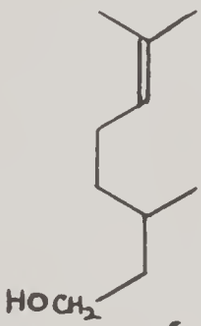
They have, with few exceptions (e.g., lavandulol, artemisia ketone), structures based on 2:6-dimethyloctane (I), formed by 1:4 addition of *iso*pentane units, and contain at least one double bond. The location of this particular double bond has occasioned much work and controversy—sometimes polemical. It is associated with the terminal *gem*dimethyl group, and for many years (1) many naturally occurring monoterpenoids were considered to be inseparable mixtures of the *iso*propenyl and *iso*propylidene forms. These views were based almost entirely on oxidative experiments, notably degradations with ozone. Typical of them was that of citronellol which was said to give, on such treatment, both acetone and formaldehyde in proportions indicating a ratio of *iso*propylidene (II) to *iso*propenyl (III) of about 4:1. It gave, nevertheless, an apparently homogeneous allophanate. A similar result was obtained with both natural and synthetic dehydrogeranic acid (2). Since attempted separation of these pairs of isomers was unsuccessful, it was proposed that either there was a labile three-centre tautomerism between the two forms, or that bond migration took place under the influence of the reagent. In the last resort, it was suggested that there might be some "abnormal" oxidation. The first view was unacceptable because of the mildness of the conditions and the known feebleness of the acidity of the hydrogen atoms involved. The second possibility was disposed of by Young and his colleagues (3), who showed that ozone-catalysed anionotropic rearrangements do not occur. They found, for instance, that partial ozonolysis of crotyl alcohol gave abnormal products, but that the recovered alcohol was unchanged. The abnormal products were, however, those that might arise from an allylic change



When the substituent, X, was a carbonyl group as in (IV), 4-hexen-3-one, the products included carbon monoxide (spontaneously



(I)



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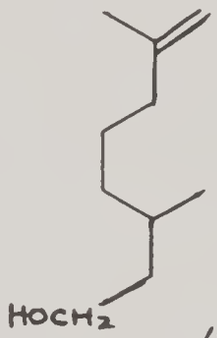


(III)

$CH_3 \cdot CH_2 \cdot CO \cdot CH = CH \cdot CH_3$

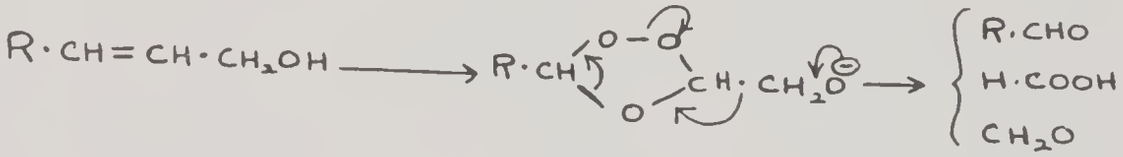
(IV)

evolved), acetaldehyde, propionic acid, and formic acid. Mixtures were also obtained on hydrogenolytic cleavage of the ozonides.

Physical methods of analysis, which have the advantage of analysing a system without disturbing the constituents, were attempted. They resulted at first in unsuccessful interpretations of ultra-violet (in the 200–230 mμ region) and Raman spectra. The further development of Raman spectra (4), however, and particularly of infra-red spectra (5) on purified materials speedily resolved the problem. It was then clearly demonstrated that despite chemical evidence to the contrary, that most monoterpenoids contained less than 2–3% of the *iso*propenyl form. This estimation, based on a band at 890 cm^{-1} ($CH_2 = CR_2$) in the infra-red is a maximum figure since other impurities could absorb in this region. Naves (6), by carefully comparing the ozonolytic and infra-red methods, found good agreement for citronellol, citronellal, citral, and other substances, but not with the allylic alcohols, linaloöl and nerol, etc. Some of the methods of purification previously used (e.g., heating with benzoyl chloride) were shown to induce isomerisation with the formation of substantial amounts of the *iso*propenyl derivative. Later investigators (7) found that ozonolysis of geraniol (known to be almost entirely in the *iso*propylidene form) afforded 25% of formaldehyde, whereas the acetate gave only a trace. These authors postulated a rearrangement of the intermediate ozonide zwitterion prior to decomposition which was dependent on the electronic effects of the allylic substituent. This hydrolytic decomposition has been, however, simply represented (8) as proceeding through the normal ozonide as shown opposite, and a similar mechanism may be operative in the decomposition of unsaturated carbonyl and carboxylic acid derivatives. It does not, however, explain the formation of carbon monoxide (3).

It must be concluded that degradative ozonolysis may give misleading results. In particular the formation of small amounts of formaldehyde should be treated with reserve (9) since they may arise from apparently stable systems.

The acyclic monoterpenoids are readily cyclised—usually by

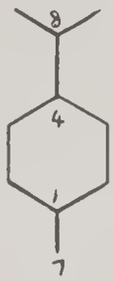

R·CH=CH·CH₂OH
R·CH
O
O
CH·CH₂O
R·CHO
H·COOH
CH₂O

acid catalysis—the process leading either to derivatives of *p*-menthane (V) or to those of 1 : 1 : 3-trimethyl*cyclo*hexane (VI); these derivatives are classified under the appropriate skeleton.

HYDROCARBONS

Myrcene (VII) was first isolated in 1895 from Bay oil, but has since been found in a number of other oils, such as those of verbena and hops. Conjugation of two of the ethylenic linkages was shown by early workers (10) by reduction with sodium and alcohol to dihydromyrcene (X), and is confirmed by the ultra-violet absorption ($\lambda_{max.}$ 224 mμ). The carbon skeleton was established by acid-catalysed hydration and oxidation to citral, whilst evidence as to the position of the double bonds was obtained by ozonolysis and oxidation to give succinic acid but no glutaric acid. Infra-red data have established the absence of *iso*propenyl isomers (11). Myrcene is obtained in 85% yield by the pyrolysis of β-pinene (XII) at 700° for 0.01–0.1 sec. (12).

Ocimene (VIII), isolated first from *Ocimum basilicum,* has probably not been obtained completely free of other hydrocarbons; it is also very susceptible to air oxidation. The conjugation of two double bonds was shown by Enklaar (13), to whom most of the earlier work is due, by reduction with sodium and alcohol to dihydromyrcene (X). The ultra-violet absorption spectrum ($\lambda_{max.}$ 237 mμ) is indicative of a higher degree of substitution than in myrcene and the disposition of the conjugated double bonds was early shown by ozonolytic experiments. Until recently (14) the formula (XI) was accepted for ocimene, but the production of 90% acetone on ozonolysis has decisively established (VIII), and this is in accord with previous work with Raman spectra (15). Heat



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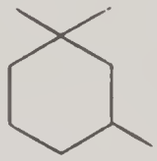

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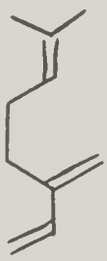

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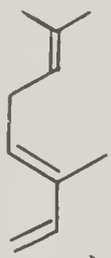

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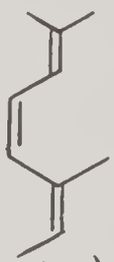

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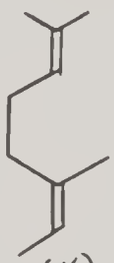
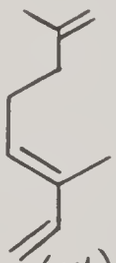
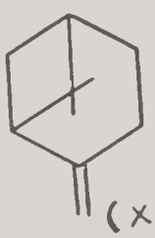


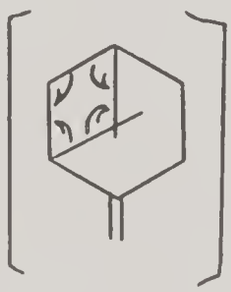
(X)



(XI)



(XII)



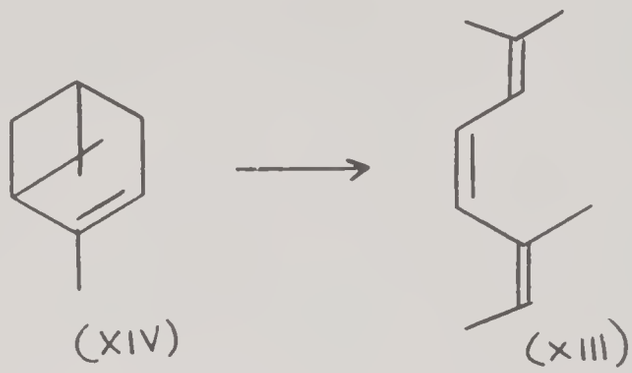
(VII)

isomerises ocimene to *allo*ocimene (XIII), which is better prepared by the pyrolysis of α-pinene (XIV). Its constitution is supported by ultra-violet spectra, oxidative degradation, and by synthesis. Claims to have separated geometrical isomers require further confirmation (16).

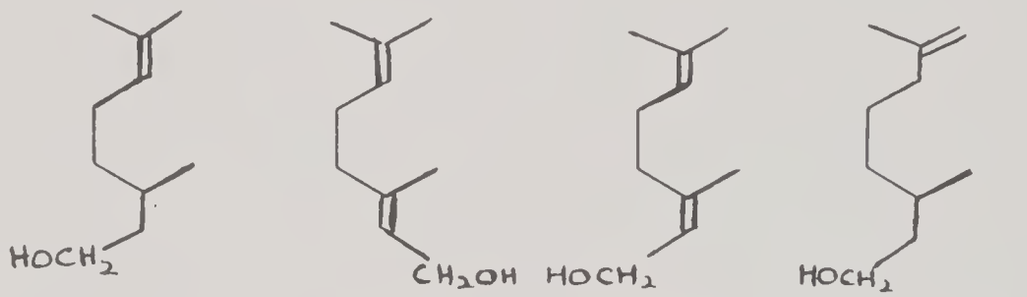
ALCOHOLS

Citronellol (XV) was first isolated in a pure condition by Tiemann and Schmidt (17), by the reduction of the corresponding aldehyde, citronellal, with sodium amalgam and acetic acid when it is obtained in the (+) form. The (–) form occurs naturally in Java citronella oil; a less usual source is the gland secretion of the alligator (18). Citronellol frequently occurs with geraniol (XVI) from which it is separated completely only with difficulty. The main features of its structure were established by oxidative degradation, which gave, as main products, β-methyladipic acid and acetone. The *iso*propylidene structure has been finally established after much controversy. Recently the *iso*propenyl compound (XVII) has been prepared, by heating citronellol at 160° with benzoyl chloride followed by saponification (a method originally used by Barbier and Bouveault to effect separation from geraniol) and fractionation. Infra-red analysis (19) showed the presence of less than 10% of (XV). Crude preparations of citronellol had previously been known as roseol and reuniol. Rhodinol, isolated from rose oil, was for a long time considered to be distinct from citronellol, but it would appear that pure rhodinol and pure citronellol are identical.

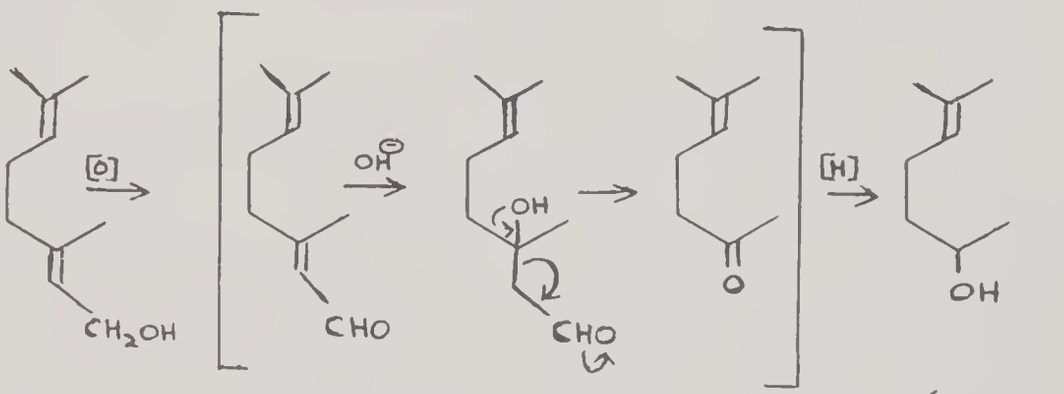
Geraniol (XVI) is found in nature both in the free state and as esters. It was first isolated in 1871 from Palmarosa oil (Turkish geranium oil), and is conveniently purified through its crystalline derivative with calcium chloride. It was characterised as a primary alcohol by oxidation to the aldehyde (mixture of *cis* and *trans*), and some of the corresponding acid. On treatment with base at 150° methyl heptenol (XVIb) is obtained, presumably by an oxidation-reduction stage (in a manner similar to the epimerisation of



(XIV) (XIII)



(XV) (XVI) (XVIII) (XVII)



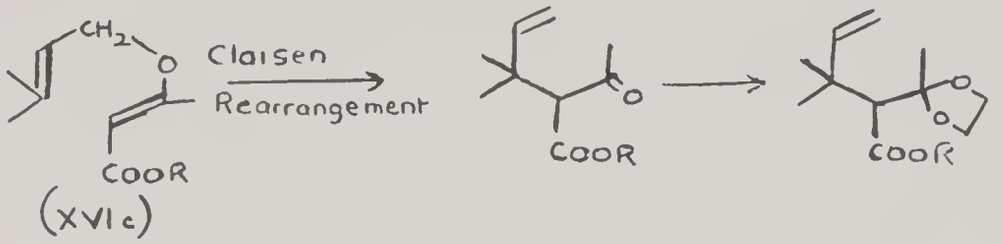
(XVIa) (XVIb)

saturated alcohols) and intermediate dealdolisation. The following elegant synthesis (XVIc) → (XVId) is due to Brack and Schinz (20).

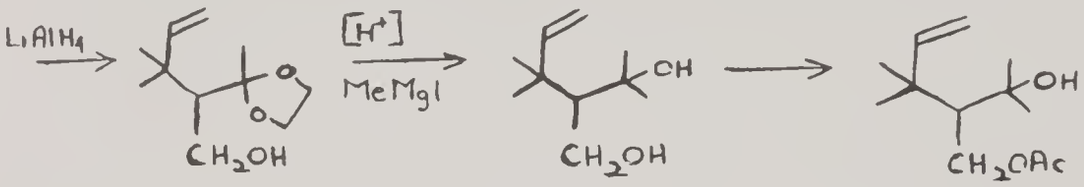
Nerol (XVIII) is the geometrical isomer of geraniol and is found in the oils of bergamot, neroli (from which it was first isolated), and petit grain, etc. It also, on oxidation, gives the citral mixture. Both geraniol and nerol undergo acid-catalysed cyclisation to α-terpineol, that of nerol being the faster, in accordance with the assigned configurations.

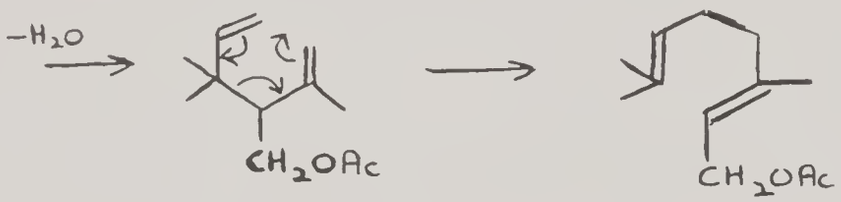
Linaloöl (XIX) isolated first in 1853 occurs both in (–) (in ylang-ylang and rose oil) and in (+) (in coriander and orange oil) forms. When prepared by the allylic rearrangement of geraniol under very mild conditions the racemic form is obtained. The reverse allylic shift also easily takes place and chromic acid oxidation, for instance, leads both to methyl heptenone and to citral, whilst with acetic anhydride geranyl acetate is amongst the products. Apart from its general behaviour as a tertiary allylic alcohol the main structure of linaloöl was established (21) by permanganate oxidation to give levulic acid and acetone. The synthesis (XIXa) → (XIX) is that of Ruzicka and Formasir in 1919. Linaloöl also undergoes acid-catalysed cyclisations and one of the most interesting of these is the formation, as acetates, of α-terpineol (XX), together with geraniol, nerol, etc., by the action of hot acetic anhydride. In this reaction, employing active linaloöl, the process of cyclisation destroys the original asymmetric centre and creates a new one; the product is, however, still optically active (23). Some degree of concertion is, therefore, indicated.

Lavandulol (XXI) occurs both in the free state and as esters in French lavender oil from which it was isolated by Schinz and Seidel. Its particular interest, biogenetically, is that it represents an example of a monoterpenoid, which is not a derivative of 2:6-dimethyloctane, i.e., of head-to-tail (1-4) coupling of *iso*pentane units. It has been suggested by Sir Robert Robinson (24) that if the C_5 unit formed by a condensation of acetate units is β:β-dimethylacrylic acid, or its equivalent, linkage takes place nor-

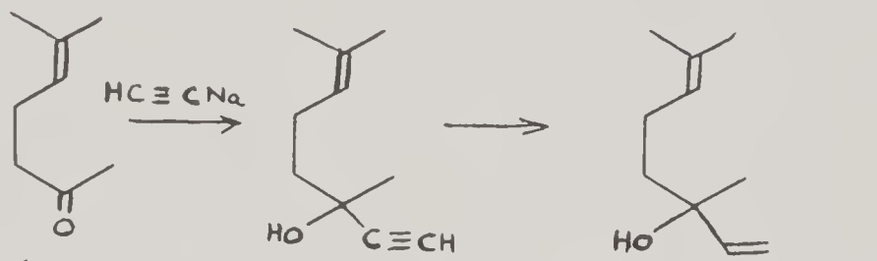


(XVIc)

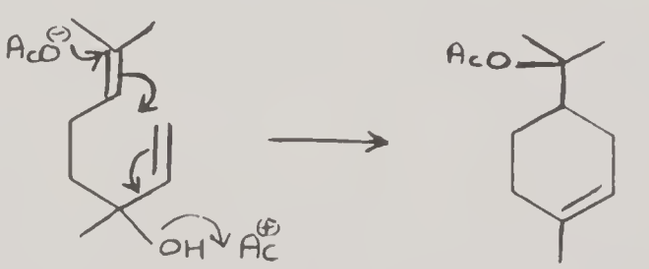




(XVId)



(XIXa) (XIX)



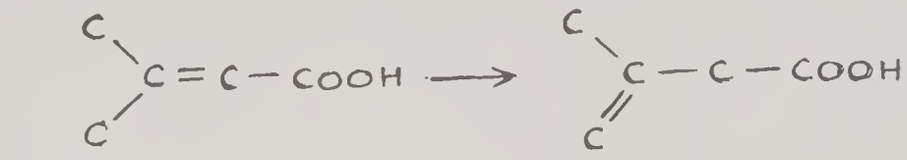
(XIX) (XX)

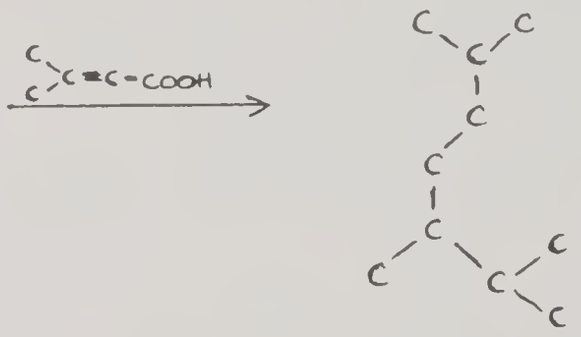
mally between the activated terminal (γ) carbon atoms of one unit and the carboxyl of the other. However, β:γ shift of the double bond then leaves the possibility of linkage at the α position. Such a linkage would lead to the lavandulol skeleton. Schinz and his collaborators have provided several syntheses of this alcohol (25), one of which is illustrated in formulae (XXa) $\rightarrow$ (XXI).

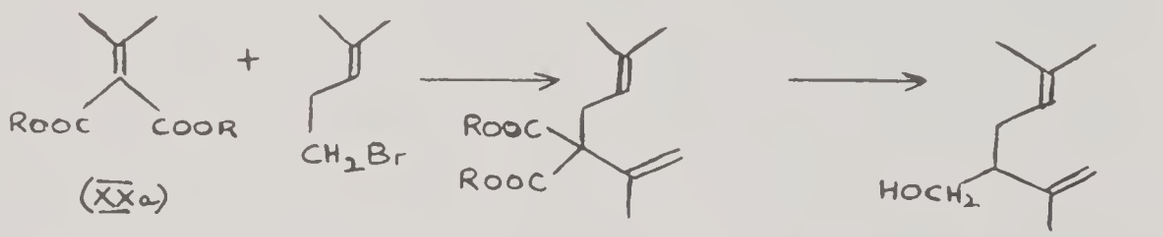
ALDEHYDES AND KETONES

Citronellal (XXII) occurs in nature, though it is not widespread, in both optical antipodes; it was first isolated from citronella oil (*Cymbopogon nardus* L.). The conclusion reached from ozonolytic and other oxidative degradations was that it consisted of 40% *iso*-propylidene and the rest *iso*propenyl in an inseparable mixture. Infra-red analysis has demonstrated again that the substance is the homogeneous *iso*propylidene compound. It may be reduced to the corresponding alcohol, citronellol (XV), with sodium amalgam, and can itself be obtained by the catalytic hydrogenation of citral. With acetone, under base catalysis (26) (XXIII), dihydro-ψ-ionone is obtained, easily cyclised to the ionone-type skeleton (page 88). Citronellal itself with acetic anhydride is cyclised to *iso*pulegol acetate (XXIV) and Semmler (27) has shown the first product to be the enol acetate (XXV).

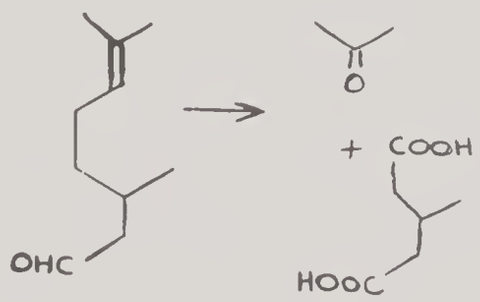
Direct conversion to *iso*pulegol is claimed to occur under the influence of light, whilst chromic acid oxidation conditions are stated (28) to give from citronellol, apart from citronellal, remarkably enough, the isomeric menthone (XXVI). The conversion of *iso*pulegol to menthone through pulegol under acidic condition is conceivable



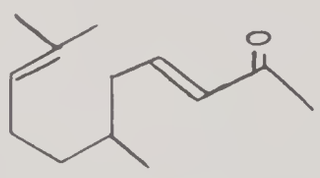




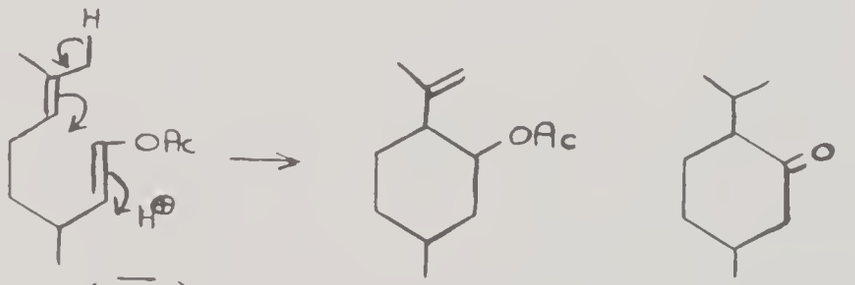
(XXa) (XXI)



(XXII)



(XXIII)



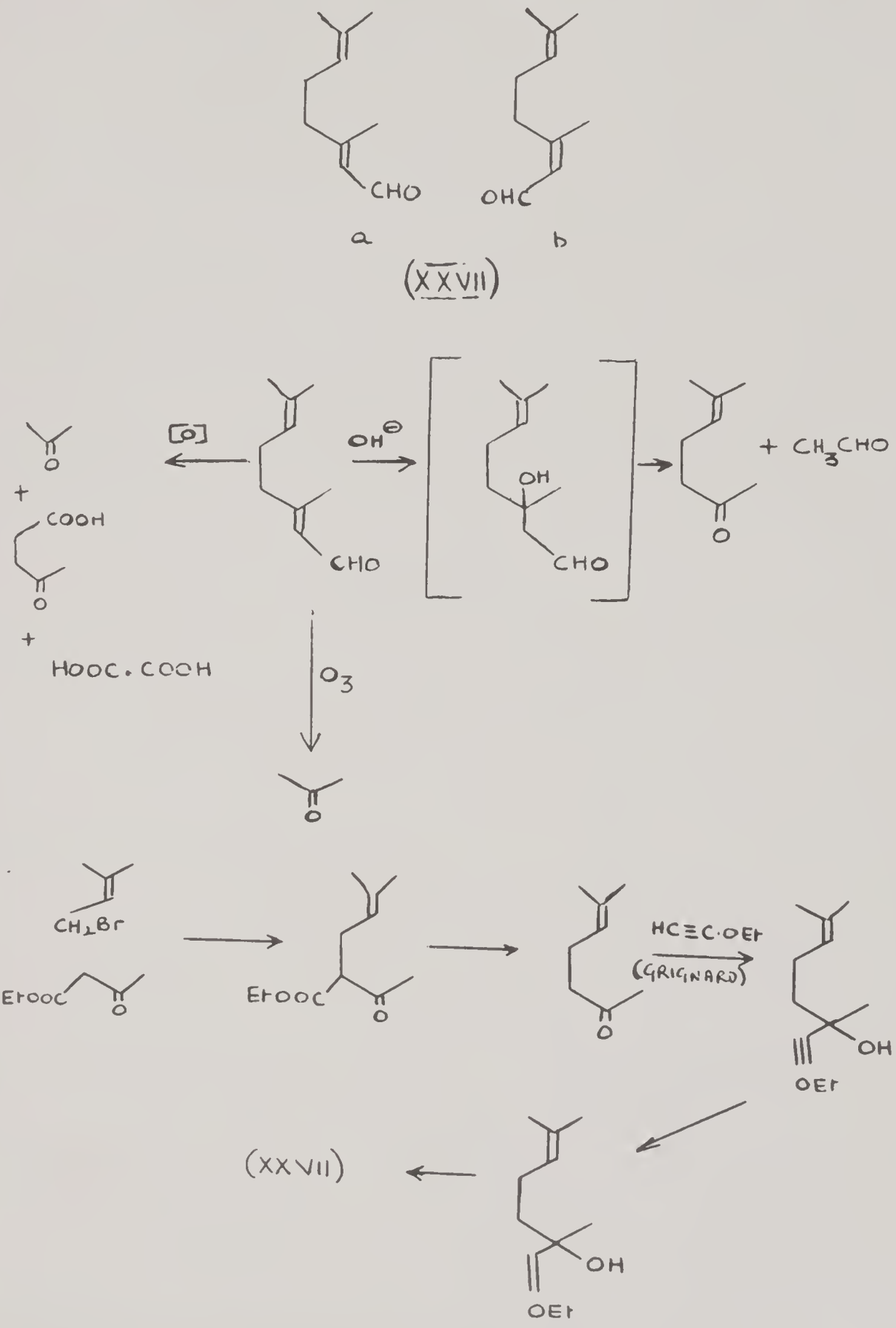
(XXV) (XXIV) (XXVI)

(35), although this has not been recorded, but it is surprising that this could compete with oxidation.

Citral (XXVII) is the most important of the aliphatic monoterpenoids and finds much industrial application. As would be expected from its formula, it exists in two geometrically isomeric forms related to geraniol (geranial (XXVIIa)) and nerol (neral (XXVIIb)), respectively. It is found in many essential oils and occurs to the extent of 80% in lemon grass oil.

The citrals have been separated by careful fractionation (29), and converted to the semicarbazones from which, however, only a mixture can be recovered on hydrolysis. The structure of citral was established essentially by the reaction scheme given opposite (30), and by oxidation to geranic acid, from which it has also been synthesised by distillation of the calcium salt with calcium formate. It has also been synthesised from isoprene hydrobromide (dimethylallyl bromide) and ethyl acetoacetate by Arens and van Dorp (31).

Citral undergoes a number of interesting base-catalysed condensations with substances containing active methylene groups. Of


CHO
OHC
a
b
(XXVII)
[O]
OH⊖
OH
CHO
+ CH3CHO
COOH
HOOC.COOH
O3
CH2Br
EtOOC
HC≡C·OEt
(GRIGNARD)
OH
OEt
(XXVII)

these, that with acetone, discovered by Tiemann and Kruger (32), to give the ψ-ionones (XXVIII), is the most important. By acid-catalysed cyclisation these lead to the industrially important ionones (see page 88). Condensation with other carbonyl compounds, including aldehydes, has been studied because of the relationship between the ionones and vitamin A. Citral may be prepared by the oxidation of linaloöl (33).

2:6-Dimethyloct-7-en-4-one (XXIX) was isolated by Jones and Smith from the volatile oil in the flowers of *Tagetes glandulifera*. Also isolated from the same source was tagetone (XXX). The structure of the latter compound was demonstrated by the reactions opposite (34), and by the absorption spectrum.

Artemesia ketone and ***iso*artemesia ketone** (XXXI and XXXII) are of interest because the structures proposed (35) represent another type of isoprene coupling.

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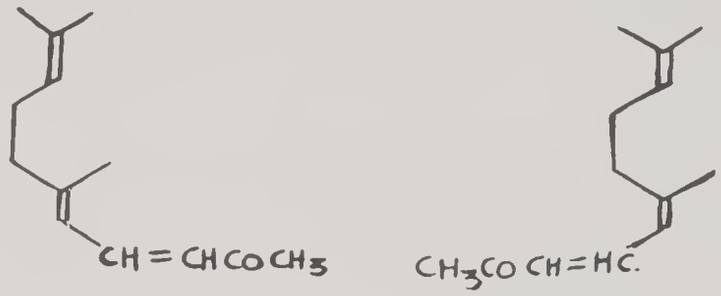
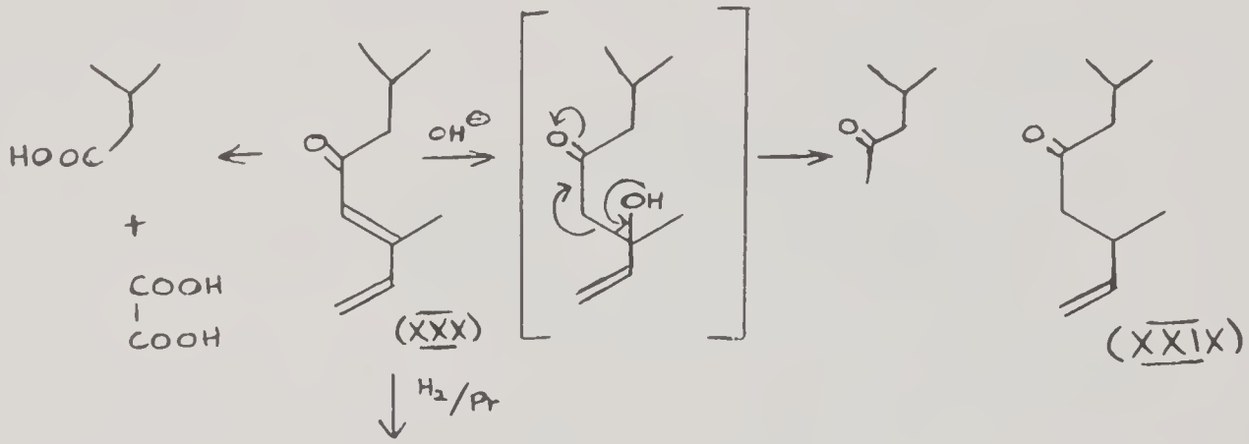
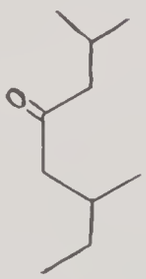


(XXVIII)



(XXX) (XXIX)



(XXXI) (XXXII)

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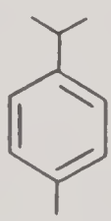
THE MONOCYCLIC MONOTERPENOIDS

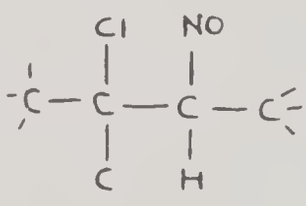
The great majority of these substances have a *p*-menthane carbon skeleton. In addition there are a small group of methylated *cyclo*hexanes and another small miscellaneous group including some derivatives of *cyclo*pentane.

Two main methods of approach to the structural problems presented by these compounds were generally employed. These were dehydrogenation and oxidation. The naturally occurring hydrocarbons, dienes in all cases, on dehydrogenation usually gave *p*-cymene (I). After identification of the carbon framework, the position of the double bonds in this framework was determined by oxidative degradation to simple aliphatic acids. Naturally occurring oxygenated substances were inter-related by oxidation and reduction, and were in turn related to the hydrocarbons by dehydration. Unfortunately, the non-specific acid-catalysed elimination of water used frequently led to mixtures. Oxidative disruption of the original oxygenated substances often gave rise to the same simple carboxylic acids as obtained by oxidation of the unsaturated hydrocarbons.

One of the major problems was the production of crystalline derivatives from these oils, which could be used both for characterization and to ensure purity in starting materials. The introduction, by Tilden (1), of nitrosyl chloride, NOCl, for this purpose was, therefore, a very considerable step forward. He found that the olefinic linkage in general reacted with this reagent to give the nitrosochloride (II). When the carbon atom bearing the nitroso group also bore a hydrogen atom isomerisation to the *iso*nitroso compound (III)



(I)



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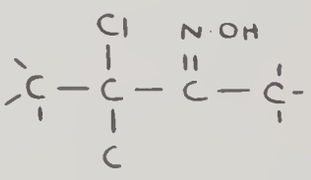
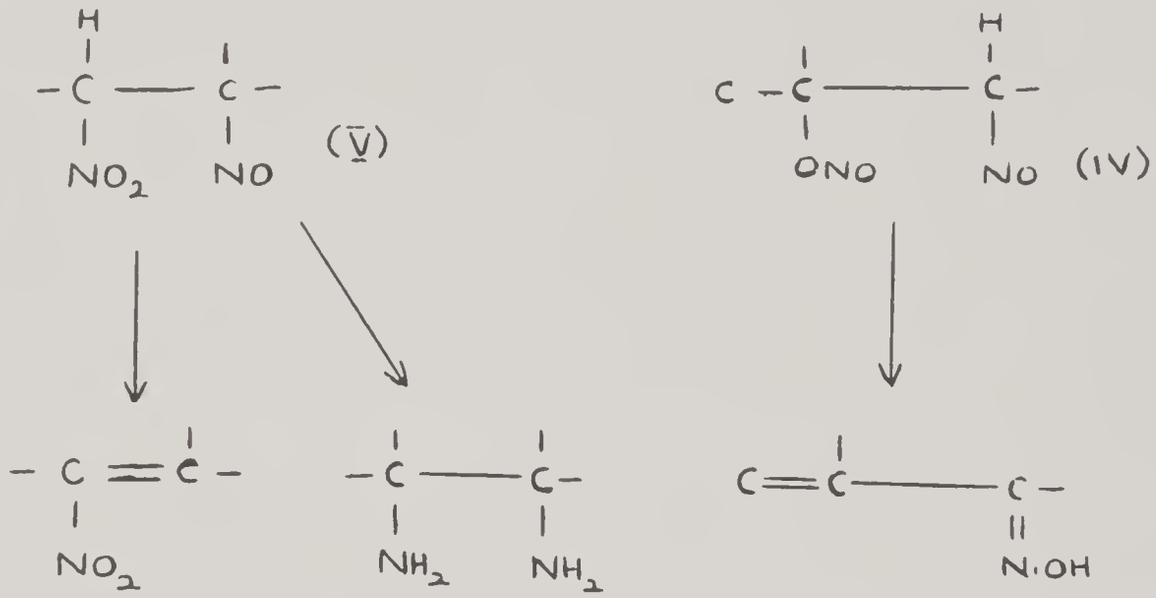


(III)

(oxime) readily took place; in the absence of this feature the nitrosochloride was stable. Provided the compound was monomeric the nitrosochloride had an intense blue colour, and so, when positive, provided a test for tetra-substituted ethylenes. The nitrosites are related substances produced by addition of the elements of N_2O_3 to the ethylenic linkage. This may be achieved by adding acetic acid to the substance in hexane solution in the presence of sodium nitrite. Two classes of products may be formed; the nitroso-nitrite (IV) or the nitroso-nitro compound (V) having properties summarised on the opposite page.

In the cyclic compounds of this series, and to an even greater degree in the higher terpenoids the problems of stereochemistry are of great interest and may be of some complexity. In recent years there have been considerable developments in this field, not only in the study of the stereochemistry of the resting molecule, but in the appreciation of the steric requirements of transition states and of reaction mechanisms in general (2). Of particular relevance to terpenoid chemistry have been investigations concerned with the stereochemistry of *cyclo*hexane rings. One of the important conclusions reached as a result of these studies is that the preferred shape or "conformation" of the mobile *cyclo*hexane ring is the "chair" (VI) rather than the "boat" (VII). The term "conformation" used in this work has been defined in several ways. The most general is: "*that a conformation is any arrangement in space of a molecule which is not superposable on any other.*" Although this implies that a molecule may have an infinite number of conformations, in fact some few are energetically preferred to the rest. The energy barriers between different conformations are, in general, so low as not to allow physical separation of conformational isomers, but exceptions, such as the resolvable diphenyl derivatives (3) do exist.

In these stereochemical investigations a new nomenclature has been evolved, applicable to all *cyclo*hexane rings whether fused to other rings or not. The bonds in a *cyclo*hexane ring (in the chair conformation) are distinguished as being of two kinds. The first form a belt of six bonds above and below the plane of the ring, and



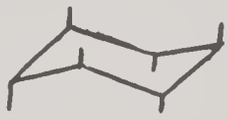
(VI)

(VII)

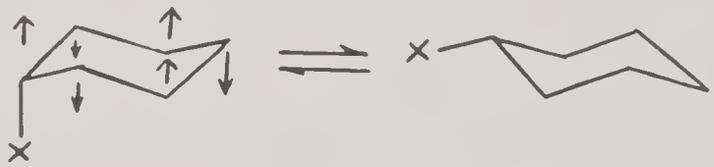
are called equatorial (e) (VIII). The second set of six bonds lie parallel to the threefold axis of symmetry of the molecule, and are termed axial (a) (IX) (in older texts the term "polar" (p) is used). One of the more important results of these investigations is the conclusion that, in general, the more bulky groups will tend to occupy the equatorial position. In a monosubstituted *cyclo*hexane this is accomplished by the simple process (IXa) ⟶ (IXb). In cases with a high degree of substitution it may not be possible for *all* bulky substituents to assume equatorial conformation. In these, and in rigid systems as found in the higher terpenoids, where direct interconversion without bond rupture is now impossible, this instability due to non-bonded interaction—i.e., the overlapping of Van der Waals' radii—is reflected both in chemical and physical properties. These include rates of reaction, reaction products, spectra, dissociation constants, etc.

In the monocyclic, flexible monoterpenoids the main stereochemical problem is that of *cis-trans* isomerism. For many years the Auwers-Skita rules (4) were employed in the allocation of configurations. These stated that, of a pair of isomers, the *cis* had the higher refractive index and density. As a result of recent work, these rules are now known to fail when applied to 1:3-disubstituted *cyclo*hexanes. A more general rule now developed is that the isomer that has the highest boiling point, highest refractive index, and greatest density is that which possesses the least stable structure (5). In conformational terms the least stable structure is that possessing the greatest number of axial substituents, it being under the greatest non-bonded stresses. The assignments so given differ from those deduced from the Auwers-Skita rules only in the case of 1:3-disubstitution where the *trans* isomer (one equatorial and one axial substituent) is less stable than the *cis* (two equatorial substituents). As an example, 1:3-*cis*-dimethyl*cyclo*hexane is more stable than the *trans* and, in violation of the Auwers-Skita rules, has the lower refractive index and density.

(VIII)



(IX)



(IXa) (IXb)

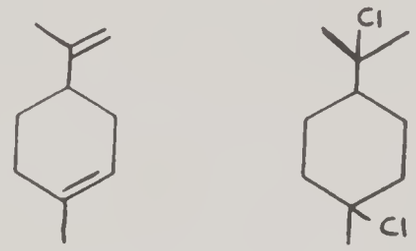
p-MENTHANE SERIES

Hydrocarbons

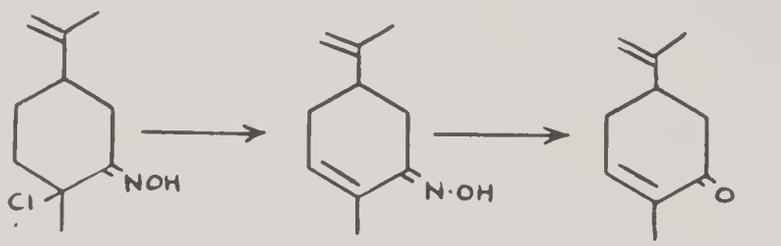
Limonene (X) is, with the possible exception of α-pinene, the most important and most commonly occurring of the monoterpenoids. It is the main constituent of the terpenoid fractions of lemon and orange oils—large quantities are produced in the citrus fruit industry—and of the oils of dill, caraway, and bergamot, etc. It is found in both the (+) and (–) forms, and also as the racemate known as dipentene.

By dehydrogenation (heating with sulphur, or bromination followed by dehydrobromination) limonene was converted (6) to *p*-cymene. Since it formed a crystalline dihydrochloride (XI) with hydrogen chloride in the presence of moisture, it was thus a *p*-menthadiene. The position of the two double bonds was then established by two methods. Firstly, with nitrosyl chloride limonene gave a mixture of two stereoisomeric colourless (dimeric) nitrosochlorides converted by hydrolysis (through the oxime (XII) and the unsaturated oxime (XIII)) to carvone (XIV). The structure of the latter had been independently established (7). Secondly, permanganate oxidation of dipentene (8) in the hands of different investigators led to a number of products amongst which the most important are terpenylic (XV) and terebic (XVI) acids.

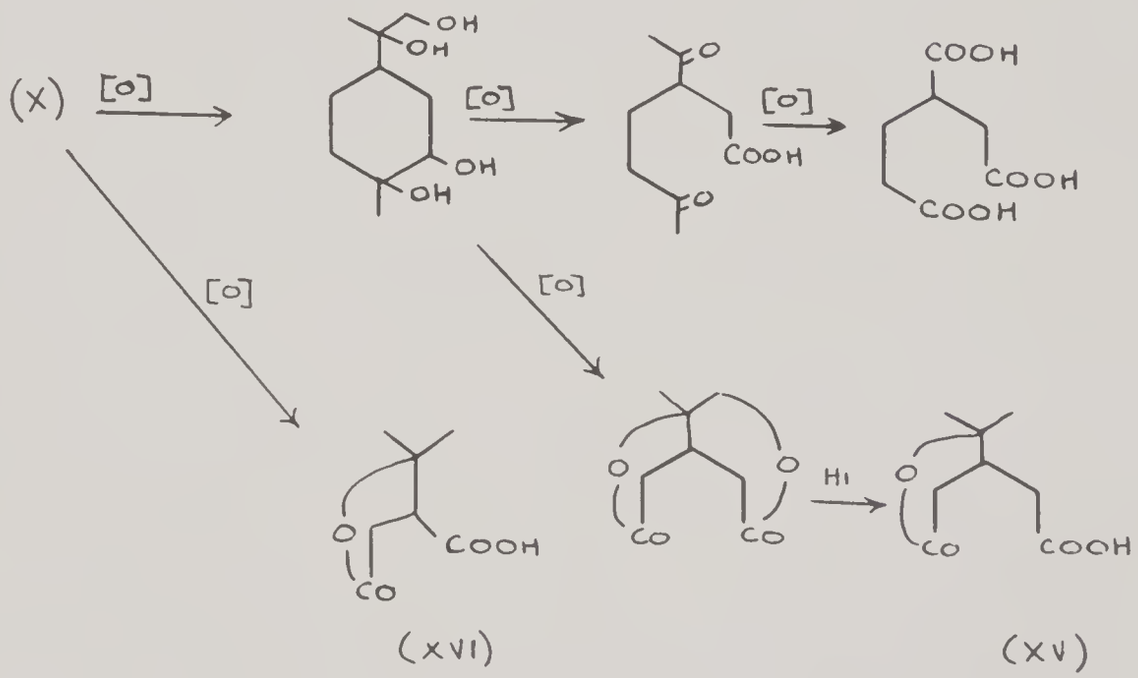
The acid-catalysed hydration of limonene has been carried out



(X) (XI)



(XII) (XIII) (XIV)

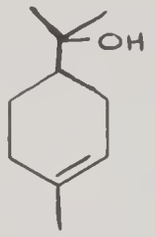


(XVI) (XV)

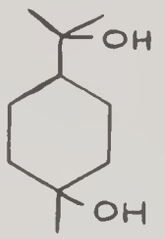
under various conditions and, for example, α-terpineol (XVII), as the acetate is obtained when the hydrocarbon is shaken with dilute sulphuric acid in acetic acid. Limonene is amongst the dehydration products of both α-terpineol and terpin (XVIII). Dipentene, the racemate, has been synthesised (9). One of the most interesting reactions of dipentene is its decomposition, by a reversed Diels-Alder, to give isoprene, which occurs when the vapour is passed over hot metal filaments. The reaction is reversible, and isoprene readily dimerises to dipentene (XVIIIa) $\rightleftharpoons$ (XVIIIb). This fact is most probably of no direct biogenetic significance since isoprene has not been found to occur naturally.

Terpinolene (XIX) also gives dipentene dihydrochloride with hydrochloric acid, but, in contrast to dipentene, the yield of isoprene on pyrolysis is very poor. That possibly only one of the double bonds differed in position from those in dipentene was suggested by the presence of terpinolene amongst the dehydration products of α-terpineol (XVII). Evidence as to the position of this double bond was obtained when Baeyer (10) found terpinolene to give a blue nitroso derivative. This was suggestive of tetra-substitution of a double bond, and this conclusion has been substantiated by oxidation to β-thujaketolactone (XX) and in other ways. Terpinolene has never been synthesised and it has probably not been obtained completely pure; its presence has been reported in coriander oil and more recently in the oil of *cupressus macrocarpa*.

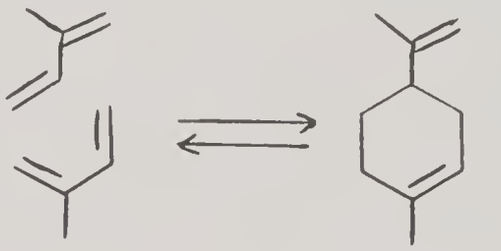
Terpinolene is easily isomerised by acids to a mixture of hydrocarbons. Amongst these are **α-terpinene** (XXI) and **γ-terpinene** (XXII) and both are produced in the mixture of dehydration products from α-terpineol. These two hydrocarbons, together with a third, **β-terpinene** (XXIII), all form the same dihydrochloride (XXIV). α-Terpinene is found in the oils of cardamom, marjoram, and coriander, etc., but has not been obtained pure; it is characterised as the nitrosite. It is formed by the digestion of linaloöl and geraniol with formic acid, and also by the dehydration of α-terpineol with oxalic acid. The proof of its constitution derives from its permanganate oxidation to (XXV) and the conversion of its nitrosite (XXVI) by sodium and alcohol reduction to a mixture of carvenone (XXVII), carvomenthone (XXVIII), and carvomenthylamine (XXIX) (11). It has



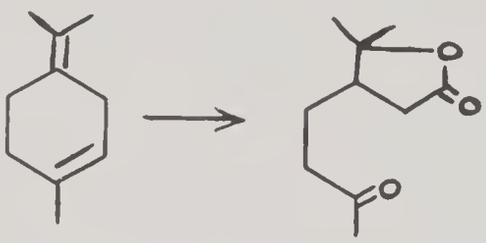
(XVII)



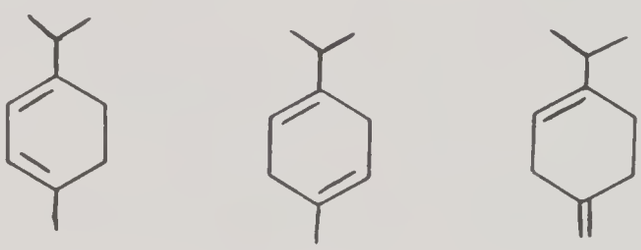
(XVIII)



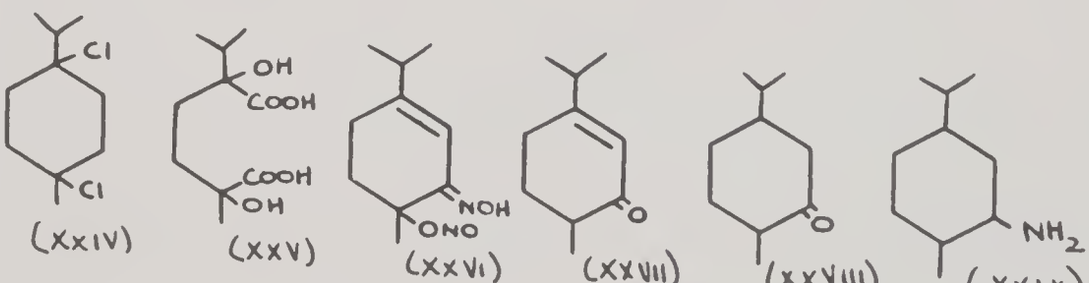
(XVIII a) (XVIII b)



(XIX) (XX)



(XXI) (XXII) (XXIII)

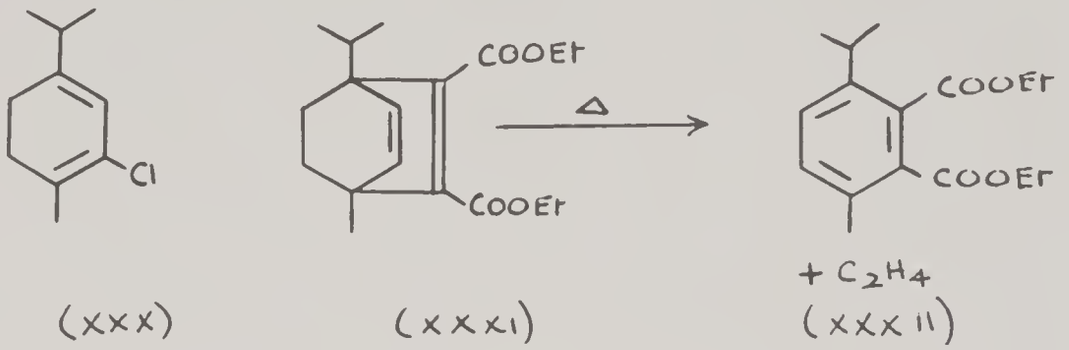


(XXIV) (XXV) (XXVI) (XXVII) (XXVIII) (XXIX)

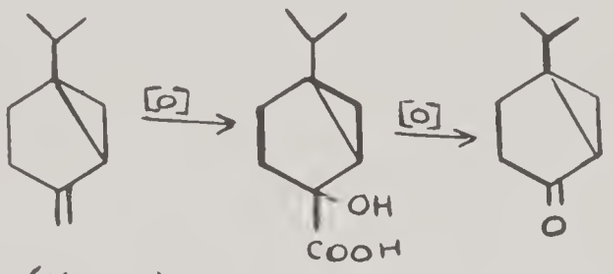
been partially synthesised from carvenone through the chloride (XXX) obtained with phosphorus pentachloride, followed by reduction with sodium and alcohol. Of particular interest is the Diels-Alder reaction with acetylene dicarboxylic ester. The adduct (XXXI), on pyrolysis, loses ethylene to give diethyl methyl*iso*propyl phthalate (XXXII) (12). This sequence is general and may be used to determine the structures of *cyclo*hexadienes. α-Terpinene has the characteristic absorption spectrum ($\lambda_{max.}$ 265 mμ) of a homoannular diene.

β-Terpinene probably does not occur naturally, but has been prepared from sabinene (XXXIII) (13). With nitrous acid on long standing some isomerisation to α-terpinene occurs. γ-Terpinene (XXII) is found, together with the α derivative, in coriander, in lemon and cumin oils, and in Ajowan oil and that of *Cupressus macrocarpa*. Largely on the basis of its formation of terpinene dihydrochloride and its oxidation products, the tetrol (XXXIV) and *iso*propyltartronic acid (XXXV), Wallach (14) proposed the formula (XXIII). This was substantiated later by a somewhat lengthy synthesis by Baeyer. It has been prepared as an application of an elegant general method of reduction of benzene rings due to Birch by the reduction of *p*-cymene with sodium and alcohol in liquid ammonia solution (15).

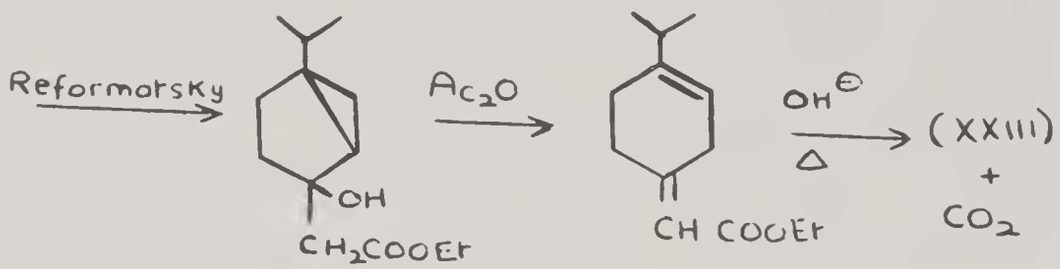
The two phellandrenes are somewhat similar in properties and were not readily distinguished by early workers, especially since there were opportunities of both geometrical and optical isomerism. **α-Phellandrene** (XXXVI) is present in the (+) form in bitter fennel oil and in elemi oil, whilst the (–) form is present in certain eucalyptus oils. It forms two stereoisomeric nitrosites both of which may be converted into the same nitro compound (XXXVII). This may be further transformed into the optically active carvotanacetone (XXXVIII) (16). Working on a mixture consisting mainly of the α-

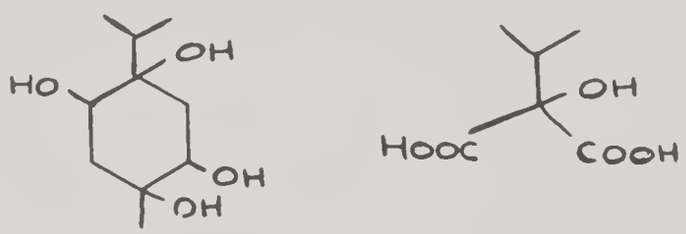


(XXX) (XXXI) (XXXII)

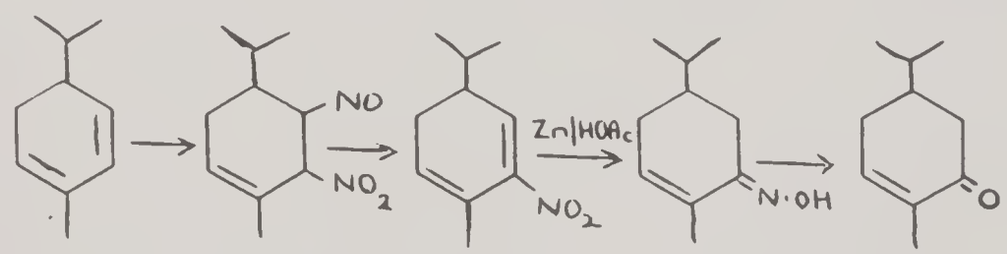


(XXXIII)





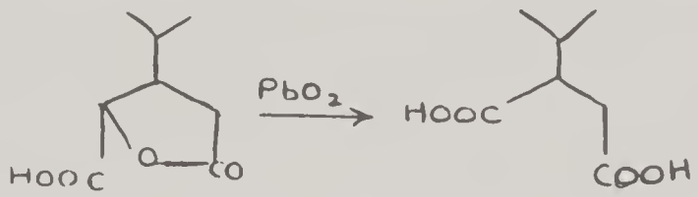
(XXXIV) (XXXV)



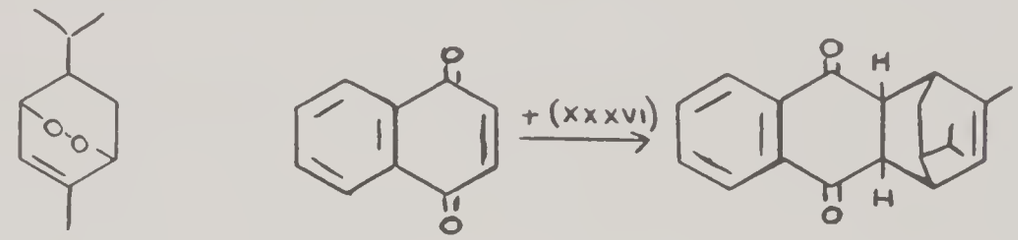
(XXXVI) (XXXVII) (XXXVIII)

isomer, Semmler (17), by permanganate oxidation, obtained the lactone (XXXIX), further oxidation then giving active (–)-*iso*propylsuccinic acid. Carvotonacetone (XXXVIII) has been converted back to α-phellandrene in a manner similar to the conversion described of carvenone to α-terpinene. α-Phellandrene, like α-terpinene, shows the expected ultra-violet spectrum ($\lambda_{max.}$ 262 mμ), and, as is common for such homoannular dienes, can be converted to a peroxide (XLI) by irradiation with visible light in the presence of suitable dyes. Another characteristic property of such dienes, the capacity to form Diels-Alder adducts, has been exploited with great ingenuity by making it serve as a proof of structure. The adduct with naphthoquinone (XLII), after air oxidation, on pyrolysis eliminates 3-methylbut-1-ene leaving 2-methylanthraquinone (18).

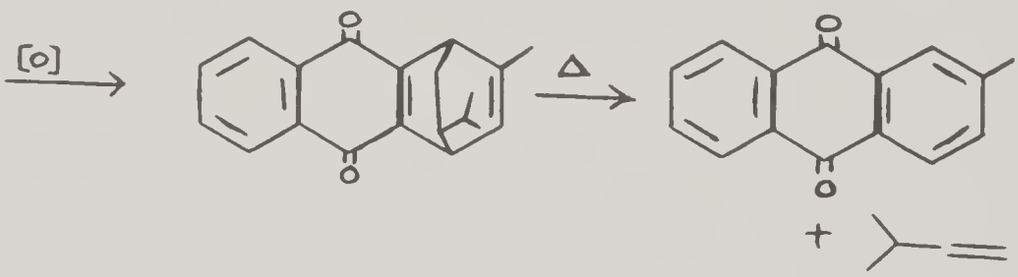
(+)-β-**Phellandrene** (XLIII) occurs in water fennel oil and in the oil from *Bupleurum fruticosum*, whilst the (–) form has been found in Japanese peppermint oil and in Canada balsam oil. It has the absorption spectrum in the ultra-violet characteristic of a transoid diene ($\lambda_{max.}$ 232 mμ). The structure of this compound was elucidated by Wallach from a study of the nitrosite which, by reactions similar to those described for the α derivative, was converted into a mixture of dihydrocuminaldehyde (XLIV) and dihydrocuminylamine (XLV). This was confirmed by Semmler by permanganate oxidation of the hydrocarbon to (XLVI) and to (XLVII). Wallach (19) showed

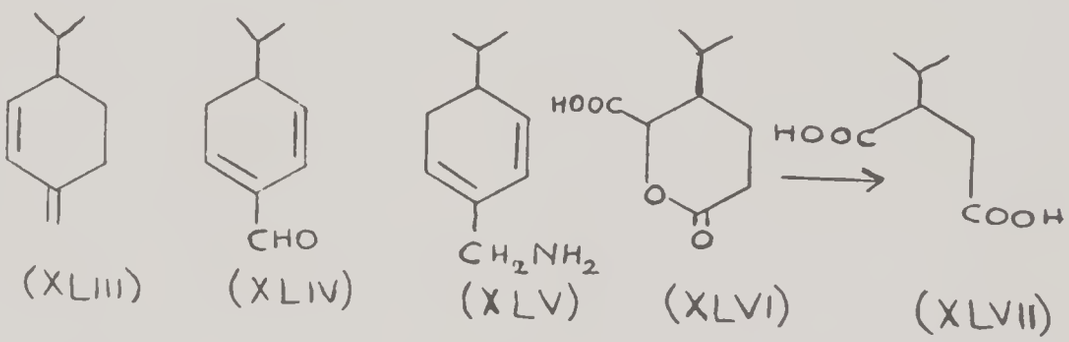


(XXXIX) (XL)



(XLI) (XLII)





(XLIII) (XLIV) (XLV) (XLVI) (XLVII)

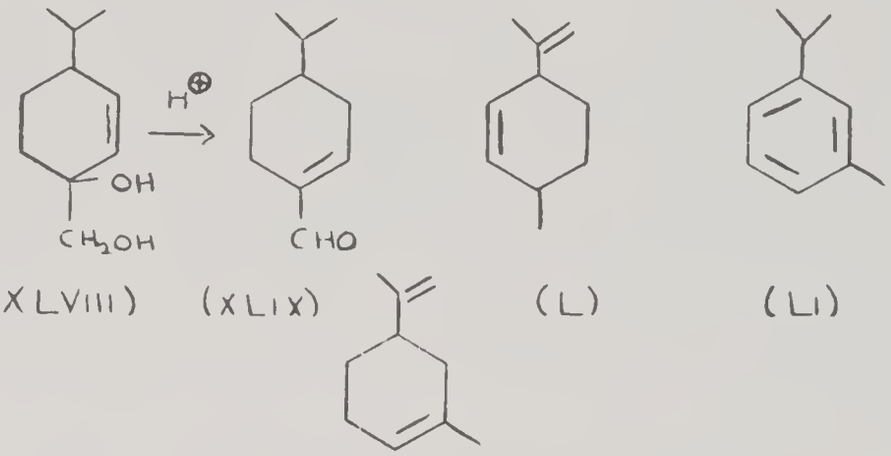
also that the primary product of oxidation was a glycol (XLVIII) which could be dehydrated and rearranged with dilute sulphuric acid to phellandral (XLIX). $\Delta^{2:8(9)}$-*p*-Menthadiene (L) is said to be amongst the terpenoids of oil of chenopodium, but further work in confirmation would seem necessary. Derivatives of *m*-cymene (LI) such as sylvestrene (LII) [carvestrene is (±)-sylvestrene] found in pine needle oil appear to be artefacts resulting from the methods of separation and are derived from bicyclic hydrocarbon precursors, the carenes (page 112).

OXYGENATED DERIVATIVES OF THE MONOTERPENOIDS

Attempts to classify the oxygenated derivatives of the *p*-menthane terpenoids must inevitably be somewhat arbitrary. They may be grouped, roughly into four classes, based on the position of the oxygen functions, but inter-conversions are facile.

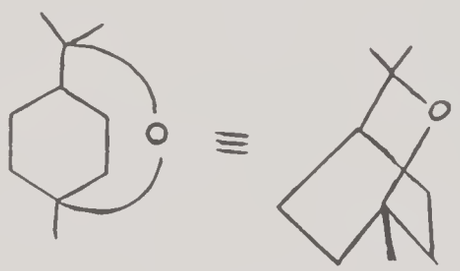
The 1:8-Cineole Group

1:8-Cineole itself is an ether (LIII) and is one of the most widely distributed of the essential oil constituents; it is found, for instance, in wormseed oil, oil of cajuput, and various eucalyptus oils. It can be purified by removal of impurities by oxidation to which cineole is very resistant. It forms remarkably stable oxonium salts (e.g., (LIV)) with the hydrogen halides, bromine, phosphoric acid and many substituted phenols, and these can be used for isolation and identification purposes. More vigorous treatment with hydrochloric acid gives dipentene hydrochloride (20). Its structure followed from its relationship to α-terpineol (XVII) and terpin (XVIII) (see below) and from its interesting oxidative degradation products (21). By the vigorous action of potassium permanganate on cineole a dicarboxylic acid (cineolic acid) (LV) was obtained. This, when heated with acetic anhydride, gave an anhydride (LVI),

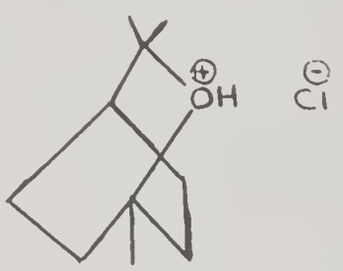


(XLVIII) (XLIX) (L) (LI)

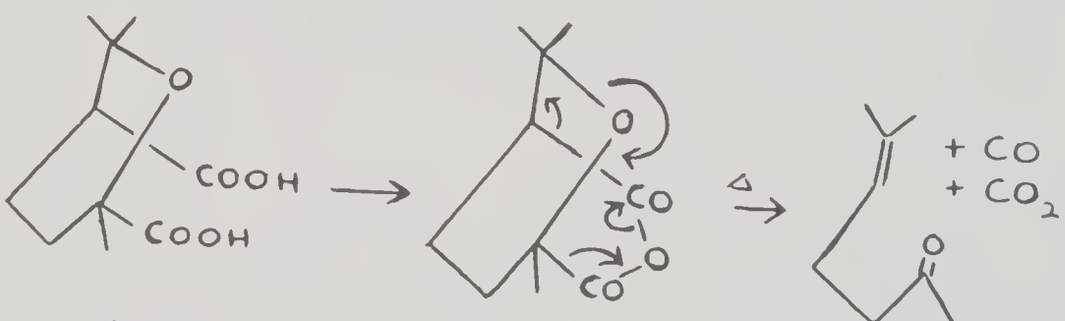
(LII)



(LIII)



(LIV)



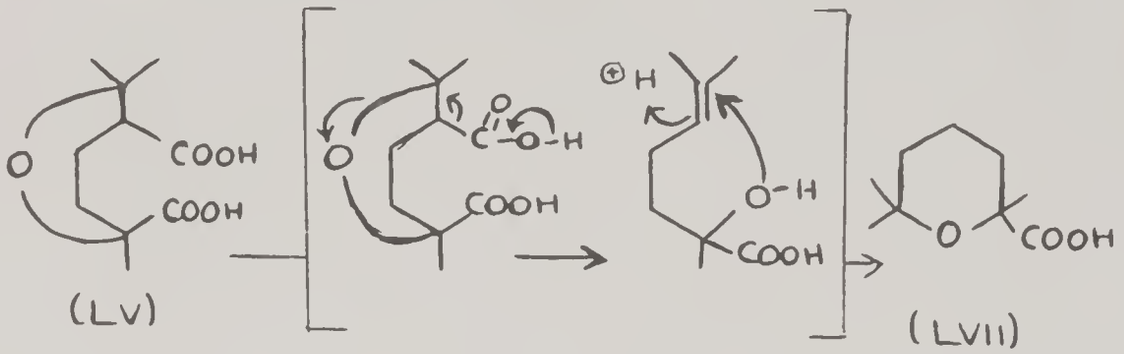
(LV) (LVI)

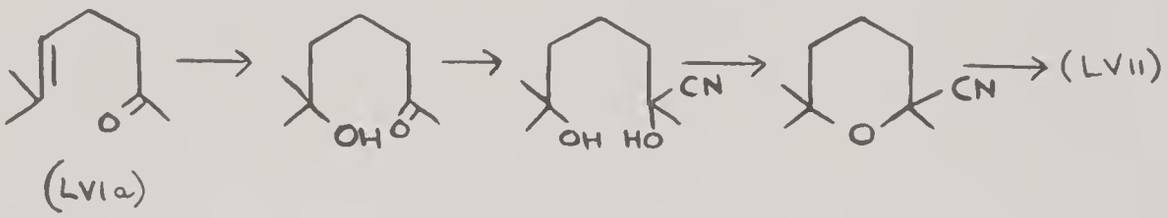
which on distillation decomposed in an unusual manner with the evolution of carbon monoxide and carbon dioxide to give methylheptenone. Heating cineolic acid (LV) under pressure with dilute sulphuric acid then affords α-cinenic acid (LVII), the structure of which has been proven by the synthesis (LVIa) → (LVII) (22).

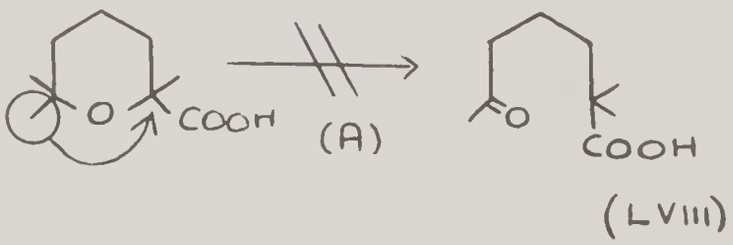
α-Cinenic acid, in concentrated sulphuric acid, undergoes an interesting rearrangement to give geronic acid (LVIII). Reinvestigation, recently, of this reaction using labelled carbon (C^{14}),has shown decisively that, regardless of intermediate steps, of the two possibilities (A) and (B) involving methyl and carboxyl transfer, the reaction takes the *second* course. The exact nature of this remarkable and so far unique transition process has not yet been clearly established (23).

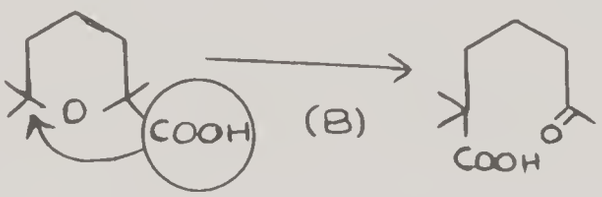
When cineole is heated with acetic anhydride in the presence of catalysts, a mixture of terpin (XVIII) and α-terpineol (XVII), as acetates, is obtained. Terpin probably does not exist in nature, being isolated as an artefact formed during working up. It exists, as would be expected, in the *cis* and *trans* forms, the former giving a stable hydrate. *cis*-Terpin is most conveniently made by the hydration of oil of turpentine using 25% sulphuric acid.

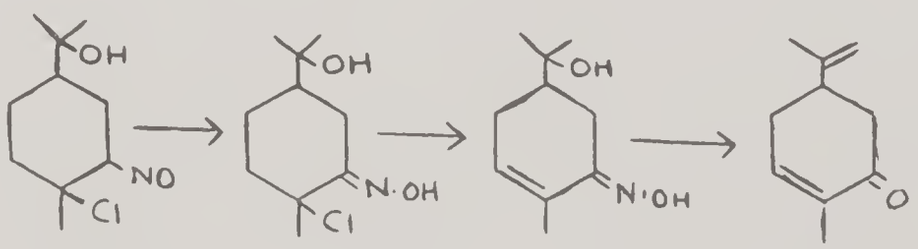
α-Terpineol (XVII) is a dehydration product of terpin, and occurs naturally, being found in the free state, and as esters, e.g., as the (+) form in neroli oil, as the (–) form in various camphor oils, and as the racemate in oil of cajuput. On dehydration it gives dipentene and, with hydrogen chloride, dipentene dihydrochloride. On oxidation terpenylic and terebic acids (XV and XVI) may be obtained, whilst formation of the nitrosochloride (LIX) gives, as shown, carvone (XIV). The nitrosochloride with alcohol gives ketocineole


COOH
COOH
(LV)
COOH
(LVII)

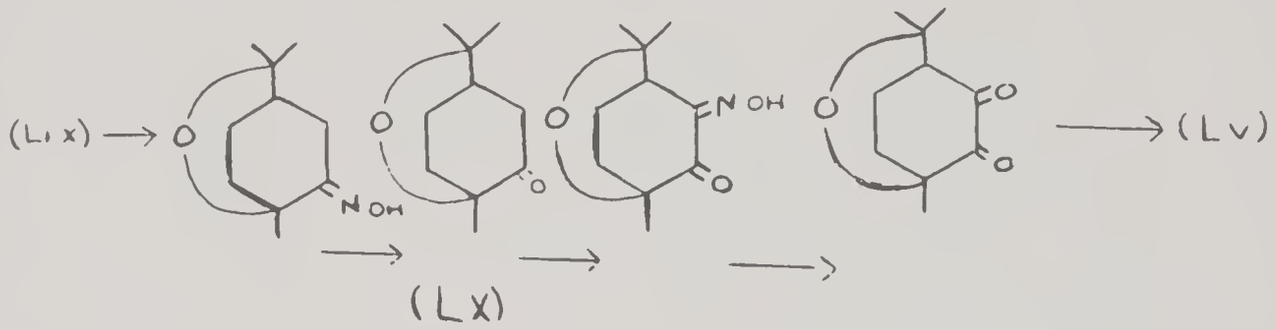

(LVIa)
CN
CN
(LVII)


COOH
(A)
COOH
(LVIII)

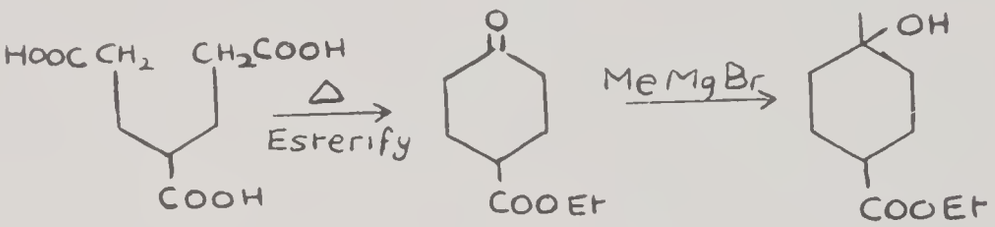

COOH
(B)
COOH

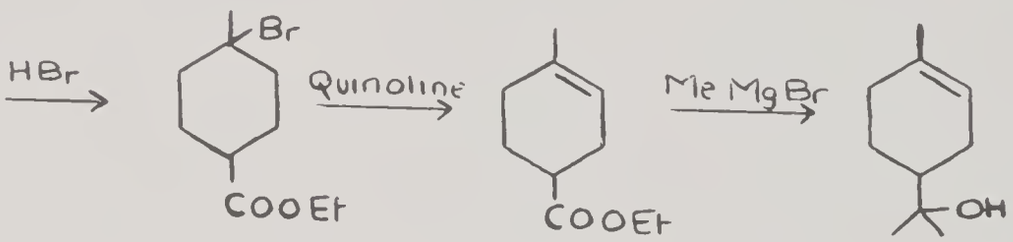

OH
NO
Cl
(LIX)
OH
N·OH
Cl
OH
N·OH
O
(XIV)

(LX), which through the *iso*nitroso compound, hydrolysis, and oxidation gives cineolic acid (LV). The total synthesis of α-terpineol by Perkin (24) confirmed its structure and therefore those of terpin, cineole, dipentene, and others. Resolution of the acid related to (LXI) afforded the active terpineol. The ester (LXI) has recently been synthesised by one-step Diels-Alder from isoprene and methyl acrylate (25). Terpineol is made commercially from pinene (page 114) by the action of sulphuric acid in acetic acid. β-Terpineol (LXII) does not occur naturally but may be obtained from the lower boiling fraction of commercial "terpineol." It may be regarded as a dehydration product of terpin as may also γ-terpineol (LXIII). The existence of the latter in nature has not been rigidly established, but it probably occurs in the leaves of *Cupressus torulosa* Don. It has been prepared from terpinolene by Baeyer, and a total synthesis has also been recorded (26).



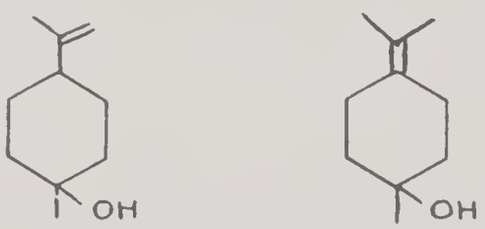
(LX)





(LXI)

PERKIN'S SYNTHESIS
OF α-TERPINEOL



(LXII) (LXIII)

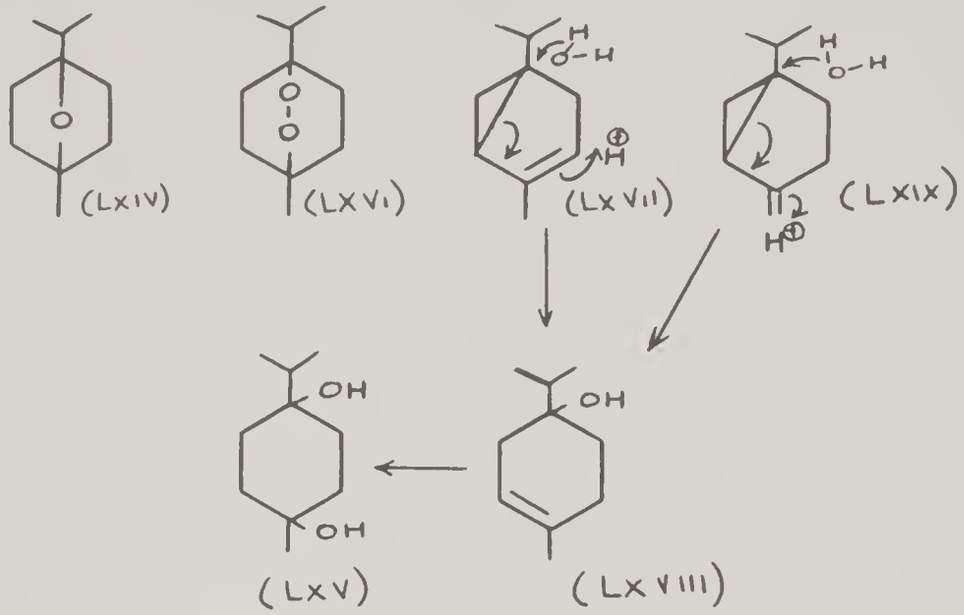
The 1:4-Cineole Group

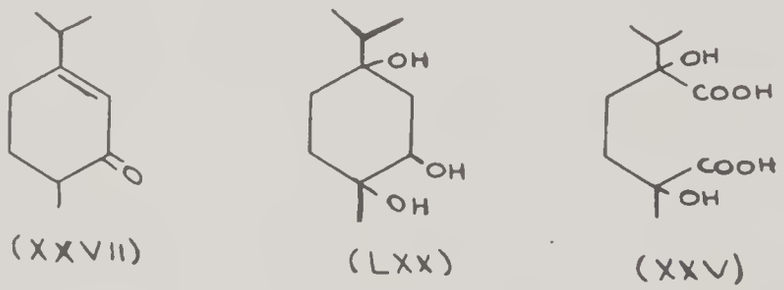
This group comprises less important substances than does the 1:8-cineole group. 1:4-Cineole itself (LXIV) is said to occur in oil of cubebs. It is obtained from the corresponding diol, *cis*-1:4-terpin (LXV), by dehydration with oxalic acid, Neither this diol, nor its stereoisomer terpinene-terpin, occurs in nature. The former is obtained by hydrogenation of ascaridole (LXVI) and the latter by acid-catalysed hydration of a number of bicyclic hydrocarbons such as α-thujene (LXVII), or *p*-menth-1-en-4-ol (LXVIII). The latter alcohol was first isolated in 1887 from cardamom oil and has also been shown to be present in marjoram oil and in certain eucalyptus oils. It is more conveniently prepared by the hydration of sabinene (LXIX). Its structure is proven by treatment of the triol (LXX) obtained by permanganate oxidation, with acid to give carvenone (XXVII). Further oxidation gives a dicarboxylic acid (XXV), obtained also from α-terpinene. *p*-Menth-3-en-1-ol was isolated by Wallach from the low boiling fraction of commercial "terpineol," but does not appear to occur in nature.

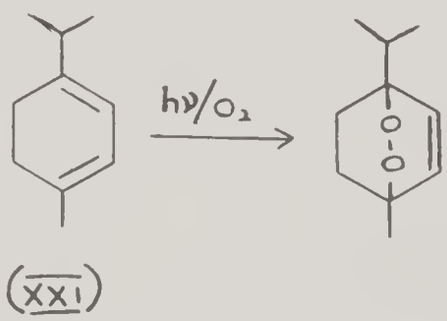
Ascaridole (LXVI) is unique as a terpenoid peroxide. This remarkable compound occurs in chenopodium oil, and has been used in the treatment of hookworm. As stated, it is hydrogenated to 1:4-terpin, but with strong acids reacts with extreme violence; on heating it explodes. It forms no crystalline derivatives. Decomposition in an inert solvent gives ascaridole glycol anhydride, an isomer, but its structure and that of its degradation products have not been entirely clarified (27). Ascaridole has been synthesised by irradiation of α-terpinene (XXI) in dilute solution in the presence of oxygen and chlorophyll (28).

The Menthone Group

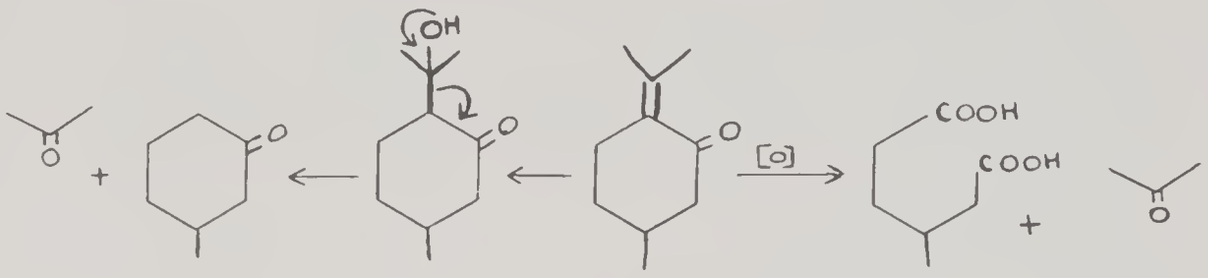
This is a large and important group increasing in stereochemical complexity from piperitenone (no asymmetric centre) through pulegone (one centre) and menthone (two centres) to menthol (three centres). The stereochemistry of all these naturally occurring compounds has been satisfactorily elucidated.


(LXIV)
(LXVI)
(LXVII)
(LXIX)
OH
OH
OH
(LXV)
(LXVIII)

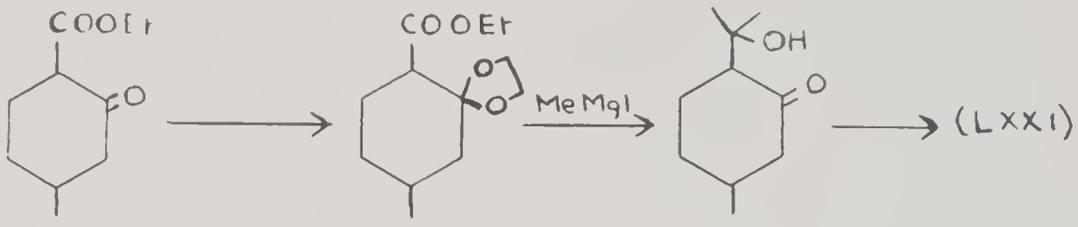

O
(XXVII)
OH
OH
OH
(LXX)
OH
COOH
COOH
OH
(XXV)


hν/O₂
(XXI)

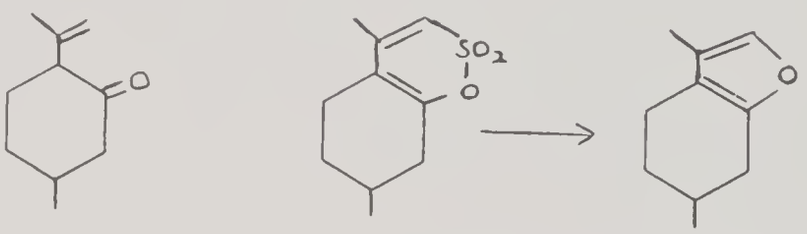
Pulegone (LXXI) in the (+) form is very widely distributed. It forms the main constituent of oil of pennyroyal. Its constitution was early established by oxidation and by hydration—dealdolisation. Its properties are in agreement with its absorption spectrum ($\lambda_{max.}$ 252 mμ) and a neat synthesis (LXXIa) $\rightarrow$ (LXXI) has recently been reported (29). Although it has been stated that *iso*-pulegone (LXXII) does not occur in nature, there is certainly an equilibrium between the $\alpha:\beta$- and $\beta:\gamma$-unsaturated substances, heavily on the side of the former. The alcohol, *iso*pulegol, may be obtained by the cyclisation of acyclic compounds (page 44). Pulegone undergoes a number of interesting transformations. With sulphuric acid in acetic anhydride it gives a sulphuric ester to which the structure (LXXIII) has been ascribed (30). On heating this loses sulphur dioxide and is converted into menthofuran (LXXIV). Menthofuran, a constituent of American peppermint oil, is a monoterpenoid member of the class of furanoid terpenoids, which includes marrubiin, vinhaticoic acid, and columbin and other substances. It is readily auto-oxidised and the nature of the oxidation product has recently been elucidated. It is (LXXV), formed through the hypothetical ozonide-like intermediate (LXXVI). Whereas (LXXV), which is faintly acidic, has no high intensity absorption maximum below 220 mμ its dehydration product (LXXVII) has a maxi-



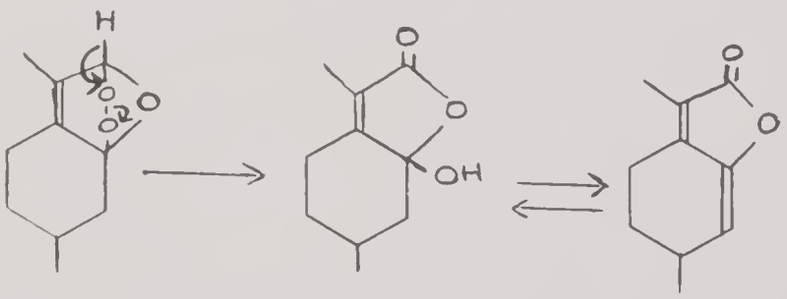
(LXXI)



(LXXIa)



(LXXII) (LXXIII) (LXXIV)



(LXXVI) (LXXV) (LXXVII)

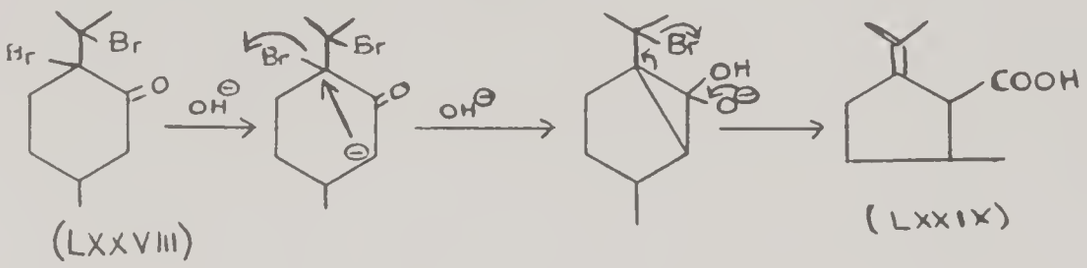
mum at 265 mμ indicative of the extended conjugation (31). Pulegone gives a dibromide (LXXVIII) which, with base, undergoes dehydrobromination and hydrolysis with rearrangement, probably by the Faworskii-type mechanism, shown to give the unsaturated acid (LXXIX) (32).

Piperitenone (LXXX), isolated from *Mentha pulegium,* is optically inactive and contains one double bond more than pulegone. Acid-catalysed dealdolisation gives acetone and methyl*cyclo*hex-1-en-3-one. It may contain a small amount of *iso*piperitenone (LXXXI).

Piperitone (LXXXII) occurs in a large number of eucalyptus oils, and the distillate from certain varieties may contain as much as 40% of the substance. Ferric chloride oxidation gives thymol (LXXXIII), whilst catalytic hydrogenation gives menthone, both products being of industrial importance. Piperitone has been prepared by the Birch reduction of (LXXXIV). The related alcohol, piperitol (LXXXV), is also found in eucalyptus oils.

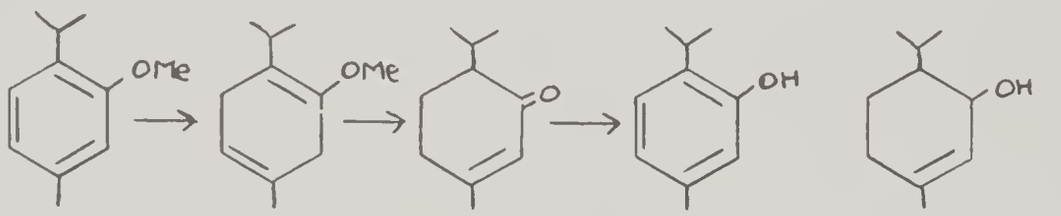
Menthone (LXXXVI) is found in peppermint oils, in geranium oil, and in oil of pennyroyal; the natural product is mainly (–)-menthone. The related alcohol, menthol (LXXXVII), also occurs in peppermint oils and has been known for a considerable time; as a mild antiseptic it has had many applications in medicine. The gross structures of menthol and menthone both follow from that of pulegone which gives menthol on reduction.

The extensive investigations, which can only briefly (33) be mentioned here, of the stereochemistry of the menthols has contributed to a large extent to the theoretical development of that subject as a whole. Menthol contains three asymmetric centres and therefore exists as four racemates named (±)-menthol, (±)-*neo*menthol, (±)-*iso*menthol, and (±)-*neoiso*menthol. (±)-Menthone contains only two asymmetric atoms and the related geometrical isomer is (±)-*iso*menthone. These may be converted into the same equilibrium mixture by any process—alkali, acid or heat—which induces enolisation of the carbonyl group. Application of the Auwers-Skita rules (see page 56) indicates that (±)-menthone is the *trans* isomer, and the assignment has been confirmed in several ways including the physical constants of the derived (by electrolytic reduction) hydrocarbons. (±)-

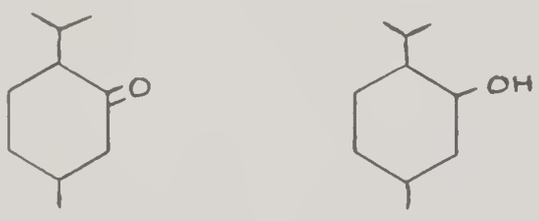


(LXXVIII) (LXXIX)

(LXXX) (LXXXI)



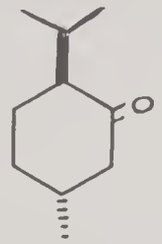
(LXXXIV) (LXXXII) (LXXXIII) (LXXXV)



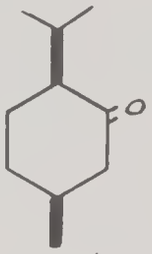
(LXXXVI) (LXXXVII)

Menthone and (±)-*iso*menthone may then be represented as (LXXXVIII) and (LXXXIX). By the hydrogenation of thymol (±)-menthol and (±)-*neo*menthol can be obtained, and by oxidation both are converted into menthone. They therefore differ in the configuration of the hydroxyl group. Similarly *iso*menthol and *neoiso*menthol have been converted to *iso*menthone. Much evidence from various sources has been adduced for the configuration of the alcohols, but some of the most powerful comes from a study of elimination reactions.

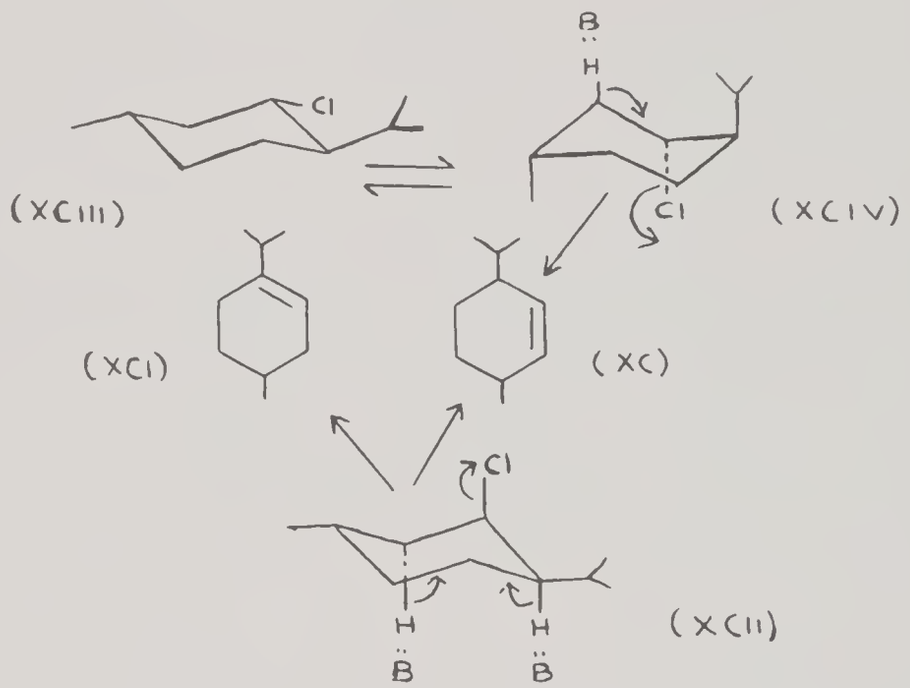
It is a conclusion established from other work that ionic bimolecular elimination reactions are much facilitated when all four centres involved in the reaction are *transoid* and in one plane (34). Now whereas menthyl chloride is stable towards weak bases (aniline, quinoline), *neo*menthyl chloride is easily dehydrochlorinated to give a mixture *p*-menth-2-ene (XC) and *p*-menth-3-ene (XCI). In the preferred conformations—conformations having the most bulky substituents in the equatorial position—of menthyl (XCIII) and *neo*menthyl (XCII) chloride it will be seen that *neo*menthyl chloride has a suitably placed hydrogen atom for *trans* elimination both at C_2 and C_4, whereas menthyl chloride would have to invert to the unfavourable conformation (XCIV) to achieve the same end. This does, in fact, take place, with the formation of *p*-menth-2-ene, when sodium ethoxide is used. Other elimination reactions have been employed to establish the hydroxyl configuration in menthol. The unimolecular pyrolysis of esters is now known to require a planar cyclic transition state (XCIVa) (35). The formation of a transition state from *cis* (equatorial-axial) substituents requires less energy than does one from di*trans* (equatorial-equatorial) substituents for, though the angle distortion required is the same in both cases, in the latter non-bonded interaction (by compression of axial hydrogen atom) is increased in achieving the planar state. In the former, on the other hand, it is decreased. Pyrolysis yields *p*-menth-3-ene and *trans*-*p*-menth-2-ene in a ratio of about 2 : 1 indicating that with the as-



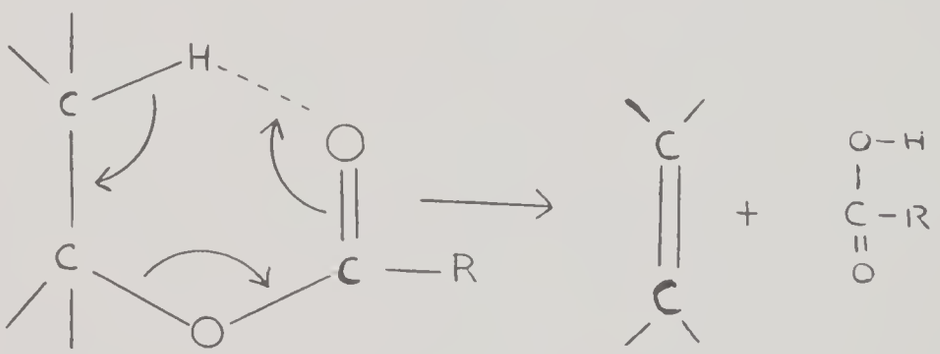
(LXXXVIII)



(LXXXIX)



(XCIII) (XCIV) (XCI) (XC) (XCII)



(XCIVa)

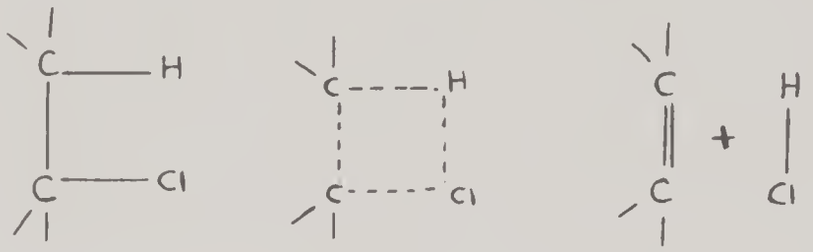
signed configurations of the hydroxyl group the major reaction is the expected *cis* elimination.

The pyrolysis of chlorinated hydrocarbons (36) requires, in a unimolecular process, a four-centre planar transition state (XCIVb), and the same requirements as those relevant to ester pyrolysis apply with regard to *cis* and *trans* hydrogen. A similar ratio of hydrocarbons was obtained on the pyrolysis of menthyl chloride as the esters.

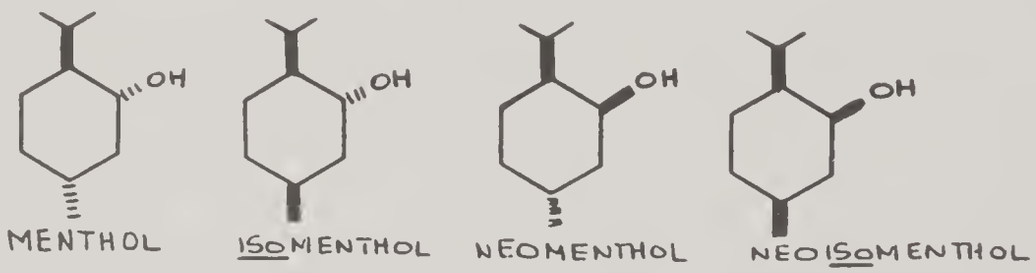
More evidence is available from rates of esterification and hydrolysis of esters, on the assumption that the equatorial alcohols esterify and hydrolyse more easily than the epimeric axial isomers, though in the flexible *cyclo*hexane system with comparatively facile inter-conversion such conclusions must be accepted with considerable reserve. Yet another approach is provided by the consideration of products of hydrogenation on the assumption of (a) *cis* addition of hydrogen to a double bond, and (b) approach of the catalyst surface from the less hindered side of the molecule. Both of these assumptions appear well founded in general organic chemistry. Piperitone gives, as would be expected, *iso*menthone, and menthone gives *neo*menthol. The final conclusions are expressed in the stereo formulae for the menthols shown opposite.

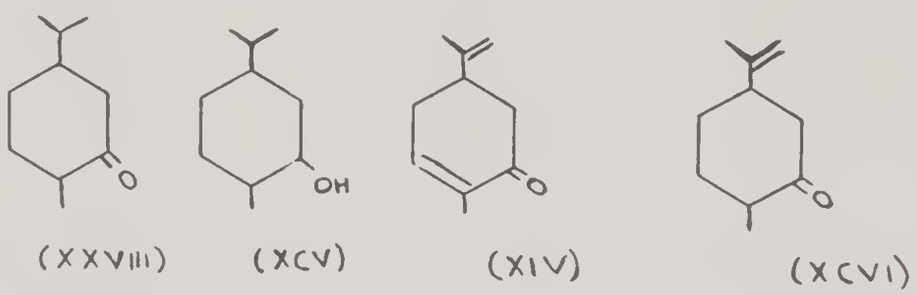
The Carvomenthol Group

Carvomenthone (XXVIII) occurs in *Blumea malcomii* and *B. enantha* and contains two asymmetric centres. It is related to *iso*carvomenthone in the same way as menthone to *iso*menthone. The related alcohol, carvomenthol (XCV), does not occur in nature, but is known in one optically active modification of all possible four racemates. Carvone (XIV), in contradistinction, is a common constituent of oils and is the main ketonic constituent of dill and caraway oils. By catalytic reduction it gives carvomenthone, whereas on electrolytic reduction in acid it gives dihydrocarvone (XCVI); the latter also occurs in caraway oil. The relation of carvone to limonene shown already through the oxime (page 58) and by the isolation of similar oxidative degradation products was confirmed by Wolff-Kishner re-



(XCIVb)



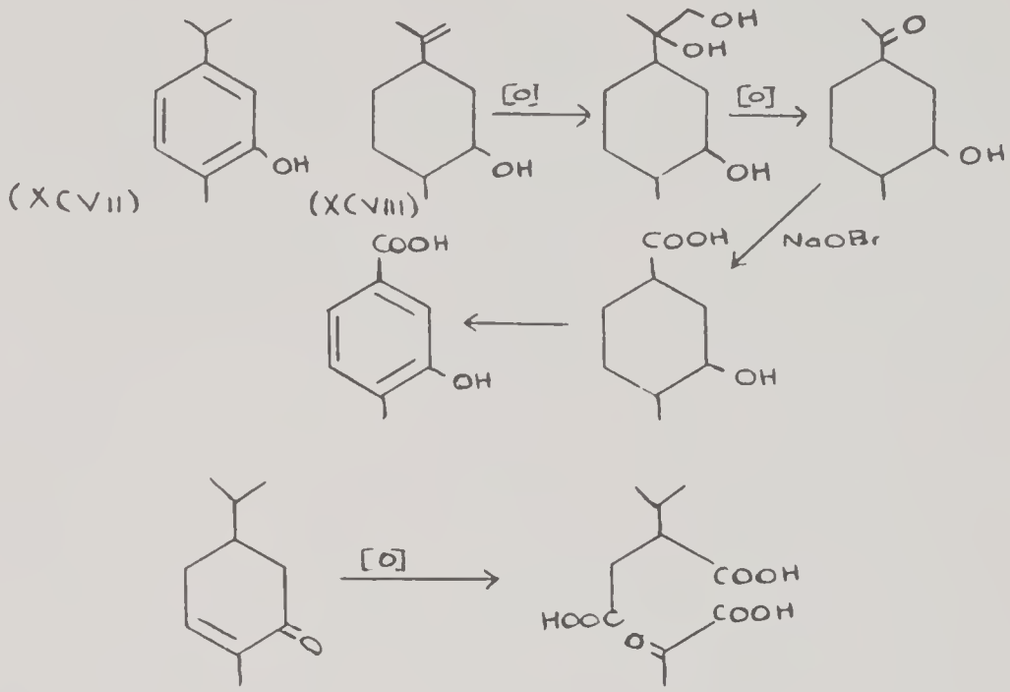


(XXVIII) (XCV) (XIV) (XCVI)

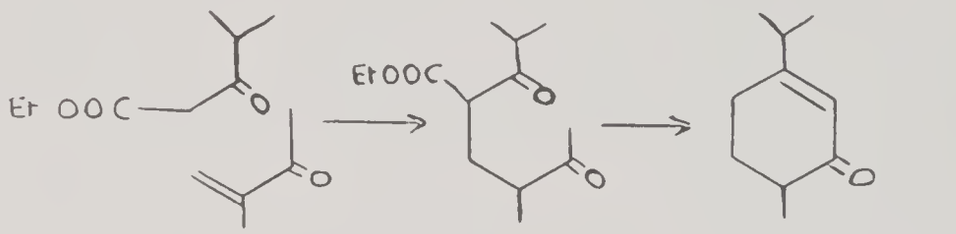
duction of the former to give the latter. Acid treatment of carvone results in facile aromatisation to carvacrol (XCVII), and this to the early workers suggested that both double bonds were in the same ring. However, the matter was resolved and the position of the non-conjugated double bond in carvone (and of the *iso*propenyl group in limonene) established by sodium and alcohol reduction to dihydrocarveol (XCVIII) and the oxidative degradation shown opposite. Reduction of carvone hydrobromide with zinc dust gives carvotanacetone (XXXVIII); this has also been found in *Blumea enantha* and *B. malcomii,* and its structure demonstrated by oxidation to pyruvic acid and *iso*propylsuccinic acid. Acid treatment of dihydrocarvone results in isomerisation to carvenone (XXVII). This has been synthesised by a method involving sodium–alcohol–liquid ammonia reduction of a carvacryl ether and also by that shown opposite (37).

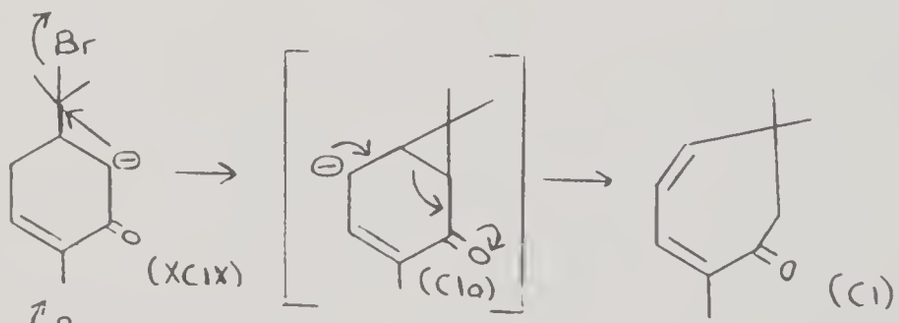
Amongst the most interesting reactions of carvone derivatives are the products of the treatment of carvone hydrobromide (XCIX) and dihydrocarvone hydrobromide (C) with base. The latter gives the bicyclic ketone carone (CII) (page 114), whilst the former gives the seven-membered monocyclic ketone eucarvone.

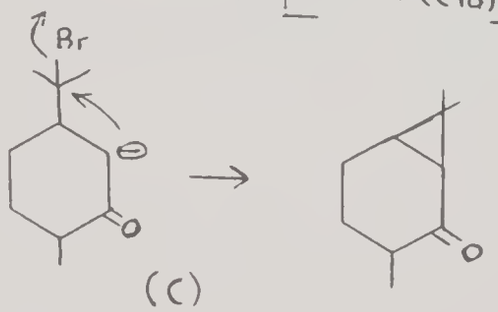
Eucarvone, which has been reported to occur naturally in *Asarum sieboldi Var. seoulensis* Nakai, was demonstrated by the reactions


(XCVII)
(XCVIII)
[O]
[O]
NaOBr
COOH
OH

[O]
COOH
HOOC
COOH

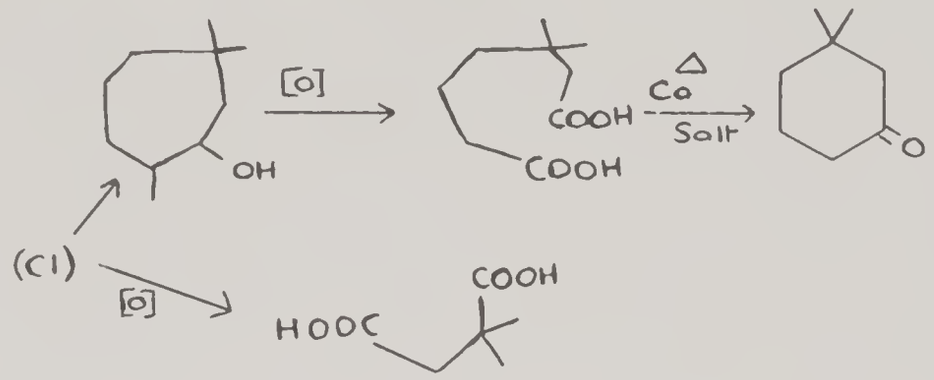

EtOOC
EtOOC
(XXVII)

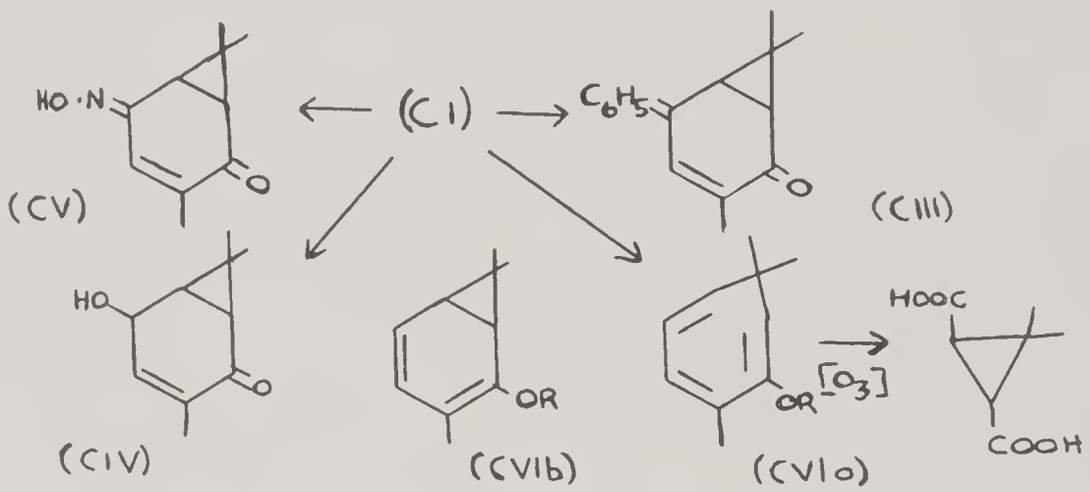

Br
(XCIX)
(C1a)
(C1)

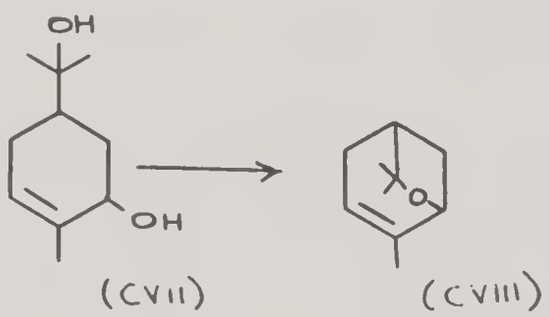

Br
(C)
(C11)

shown opposite to be monocyclic (38). Recent work has shed more light on the ease with which isomerisation may take place. Thus the product of reaction of benzaldehyde, assumed by Wallach to provide evidence of a methylene group α to the carbonyl function, so indicating a monocyclic structure, has been shown (39) to be (CIII) and bicyclic. The action of selenium dioxide is to introduce a hydroxyl group (CIV), again with cyclisation, whilst sodium eucarvone with butyl nitrite gives the oxime (CV). Treatment of sodium eucarvone with acid chlorides led, however, to monocyclic enol esters (CVIa). These structures are ring-chain tautomers of the structures (CVIb), and confusion was created by the production of *cis*-caronic acid on ozonolysis. However, nuclear magnetic resonance data unequivocally indicated (CVIa), since there was no absorption in the region expected for the tertiary bridge hydrogen in a caradiene structure. Eucarvone itself, from ultra-violet data, contains only an infinitesimal amount of the bicyclic structure (CIa) since no maximum characteristic of the $\alpha:\beta$-unsaturated ketone could be detected. Its presence in minute amount was shown, however, by deuterium exchange experiments. In sodium ethoxide-deuteroethanolic solution *three* hydrogens instead of the expected two were exchanged.

The formation of carene derivatives, as reaction products, from eucarvone could proceed by reaction of the anion (or enol) of the bicyclic form, or by a process in which cyclisation and substitution are simultaneous, or by a process between these extremes. The formation of eucarvone from carvone hydrobromide (XCIX) could in principle involve the intermediate carenone (CIa) or proceed by a concerted elimination-rearrangement process. The most recent work (50) has resulted in the isolation of (CIa) and established the correctness of the first course. A final member of the carvomenthol group is **sobrerol** (CVII) which is, surprisingly, a product of the air oxidation of α-pinene in sunlight. By the action of acid it is converted to pinol (CVIII).


[o]
OH
COOH
COOH
Ca
Salt
O
(CI)
[o]
COOH
HOOC


HO·N
O
(CV)
(CI)
C6H5
O
(CIII)
HO
O
(CIV)
OR
(CVIb)
OR
[O3]
HOOC
COOH
(CVIa)

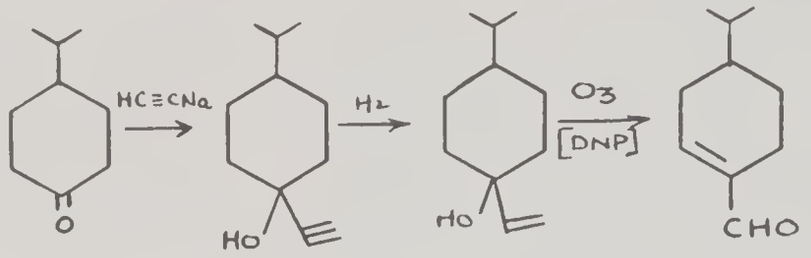

OH
OH
O
(CVII)
(CVIII)

A few terpenoids of the *p*-menthane group are known which have the C_7 position oxygenated. Amongst these is **phellandral** (CIX), which is found in both optical antipodes in water fennel oil and in various eucalyptus oils. It has been synthesised, a recent route being that shown opposite. **Perillyl alcohol** (CX) is found in ginger grass oil and bergamot oil, and the related aldehyde, **perillaldehyde** (CXI), in *Perilla nankininensis* Decne. Perillyl alcohol can be converted to the chloride which, on reduction with sodium and alcohol, gives limonene. **Cryptone** (CXII) is not strictly a terpenoid but is a closely related substance. It was first obtained by Wallach by the air oxidation of β-phellandrene, but has since been found in various eucalyptus oils and in water fennel oil.

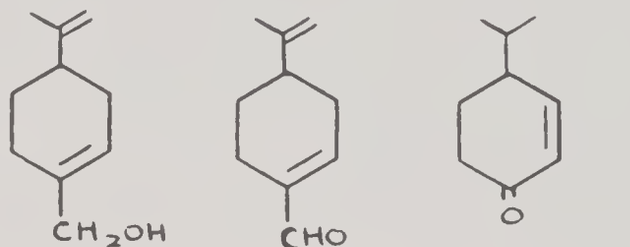
Diosphenol (CXIII), is obtained from buchu leaves, It is acidic, as would be expected from its enolic structure, and gives an intense green colour with ferric chloride. Its structure follows from the reactions shown opposite (40). It is also obtained from piperitone and carvenone by mild permanganate oxidation and from menthone by air oxidation in the presence of ferric ion. Although it contains an asymmetric centre, the product, as isolated, is optically inert, because of the facile racemisation at the asymmetric centre which is α to a carbonyl group. Some evidence, not as yet compelling (41), has been adduced for the existence of the other tautomeric forms of diosphenol.

THE METHYLATED CYCLOHEXANE GROUP

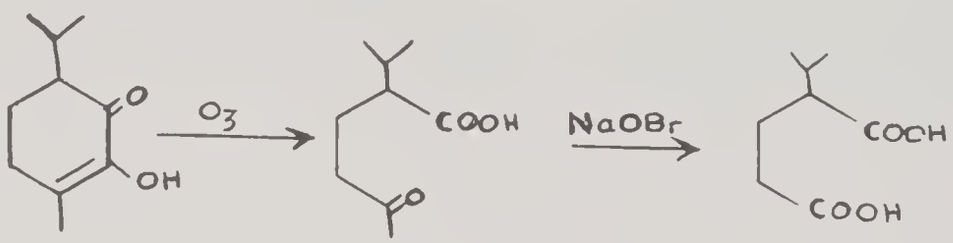
Cyclocitral is typical of these. This particular example cannot, however, be obtained by direct acid cyclisation of citral, as this leads to *p*-cymene. Preliminary condensation with an aromatic base, on the other hand, followed by cyclisation and subsequent hydrolysis gives a mixture of α- (CXIV) and β- (CXV) *cyclo*citrals (42). Similar derivatives have been obtained from other substances such as geraniol, geranyl acetate, lavandulol, dihydromyrcene, etc.



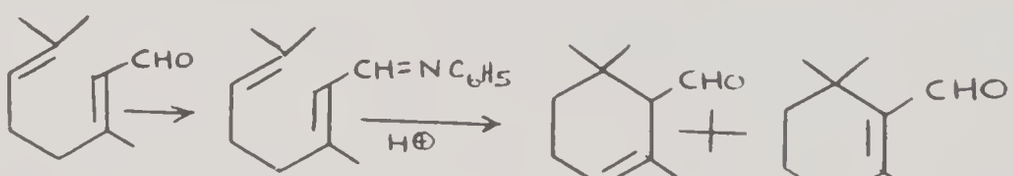
(CIX)



(CX) (CXI) (CXII)



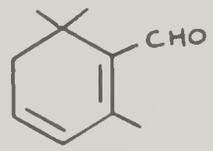
(CXIII)



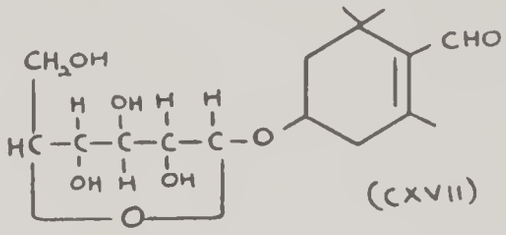
(CXIV) (CXV)

Safranal (CXVI) is a natural product related to *cyclo*citral; it is the aglycone of the bitter principle picrocrocin from saffron (*Crocus sativus*). It has also been obtained (43) by the oxidation of β-*cyclo*citral with selenium dioxide. Picrocrocin probably has the structure (CXVII), since the compound has the absorption of an unsaturated aldehyde and splits glucose—presumably by β-elimination—with alkali. Of greater industrial importance are the ionones, which are obtained by the cyclisation of ψ-ionone (page 48). They may be prepared, also, by the condensation of α- and β-*cyclo*citral with acetone. Their structures were elucidated, before the methods of absorption spectroscopy were available, by Tiemann, using oxidative methods as shown (44).

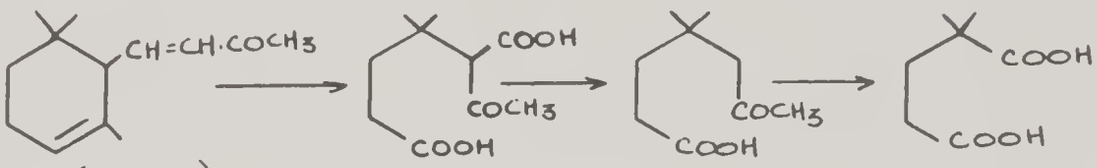
α- (CXVIII) and β- (CXIX) **ionone** occur in the essential oil of *Boronia megastigma*, and in costus oil. Dihydro-γ-ionone (CXX) has been isolated from ambergris whilst (CXXI) has been shown to be present in the urine of pregnant mares and the scent glands of the Canadian beaver. The acid-catalysed cyclisation of ψ-ionone and related compounds is not, however, restricted to formation of ionone-type substances. Under various conditions other products



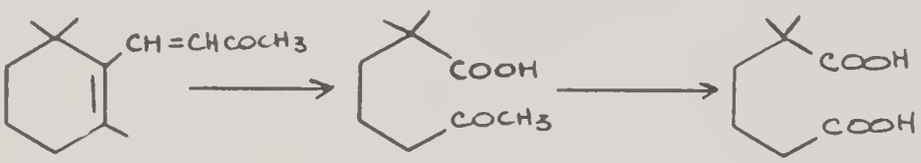
(CXVI)



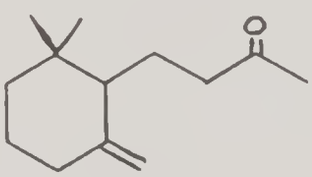
(CXVII)



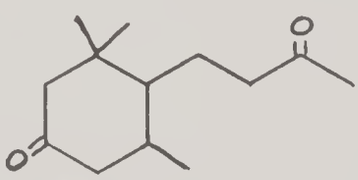
(CXVIII)



(CXIX) (LVIII)

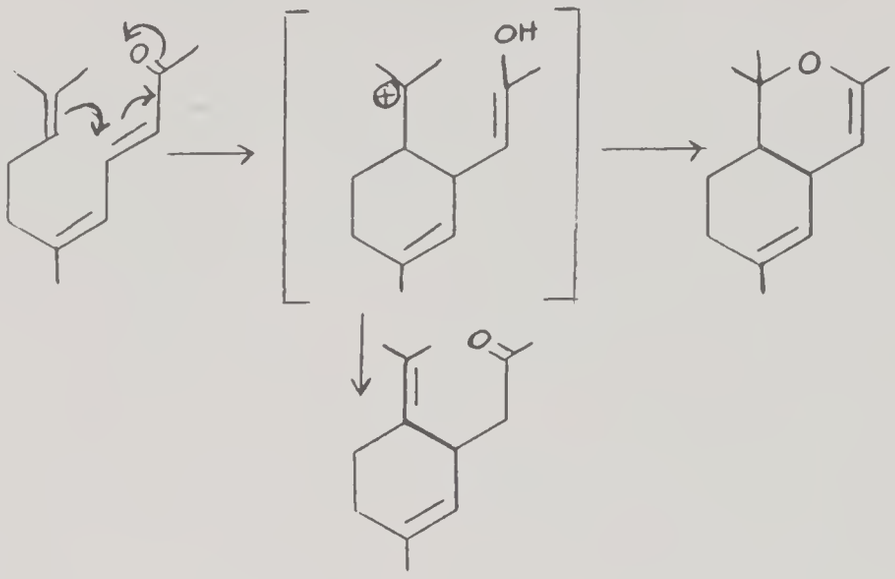


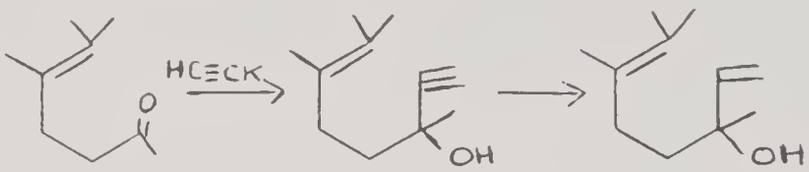
(CXX)

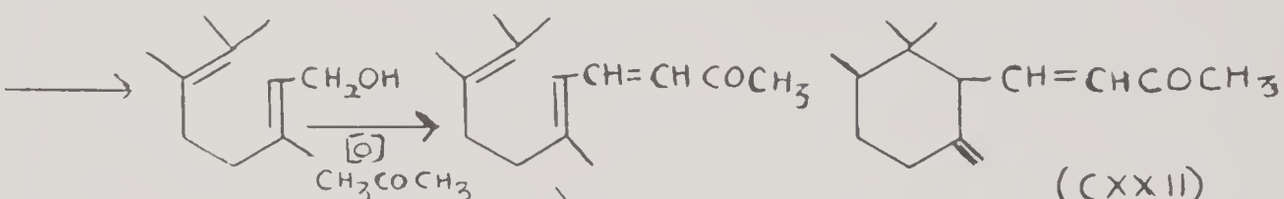


((CXXI)

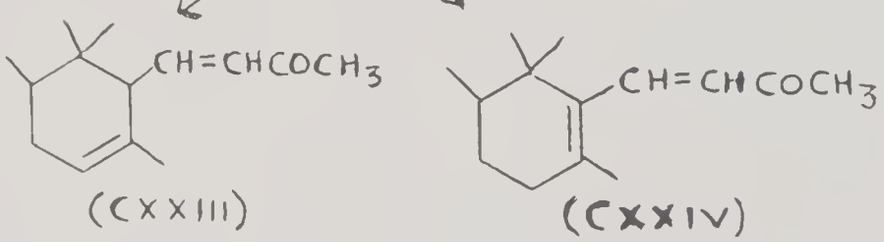
may be obtained and illustrative are the products of boron trifluoride-catalysed cyclisation shown on the opposite page (45). The ionones are used extensively in the perfume industry. Irone (CXXII), found in the oil of orris root, is structurally related to the ionones, but contains one more carbon atom. It is also much used in perfumery. The γ-isomer (CXXII), probably the main constituent of the oil, is isomerised to α- (CXXIII) and β-irones (CXXIV) with acids. A number of syntheses have been achieved; that illustrated is due to Ruzicka and his collaborators (46). The ionones are of particular interest because of their structural relationship to vitamin A (for which they have been a synthetic starting material) and to the carotenes. A more recently isolated substance, Shonanic acid (CXXV), is also related to the irones.



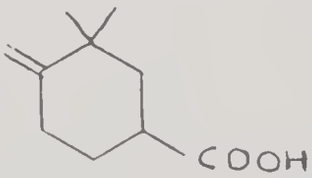




(CXXII)



(CXXIII) (CXXIV)

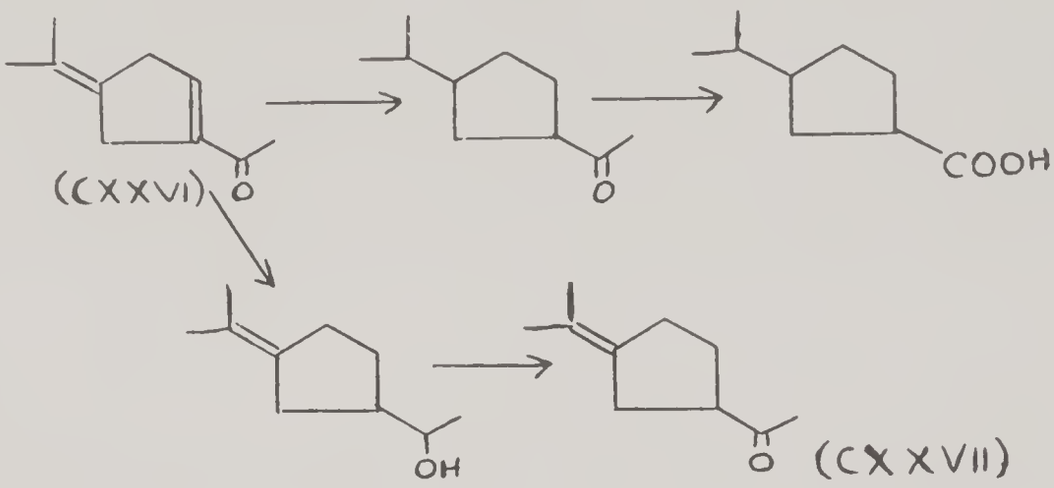


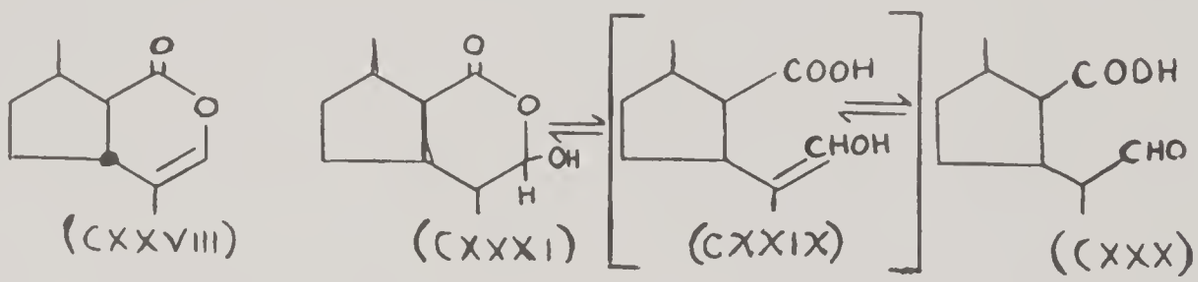
(CXXV)

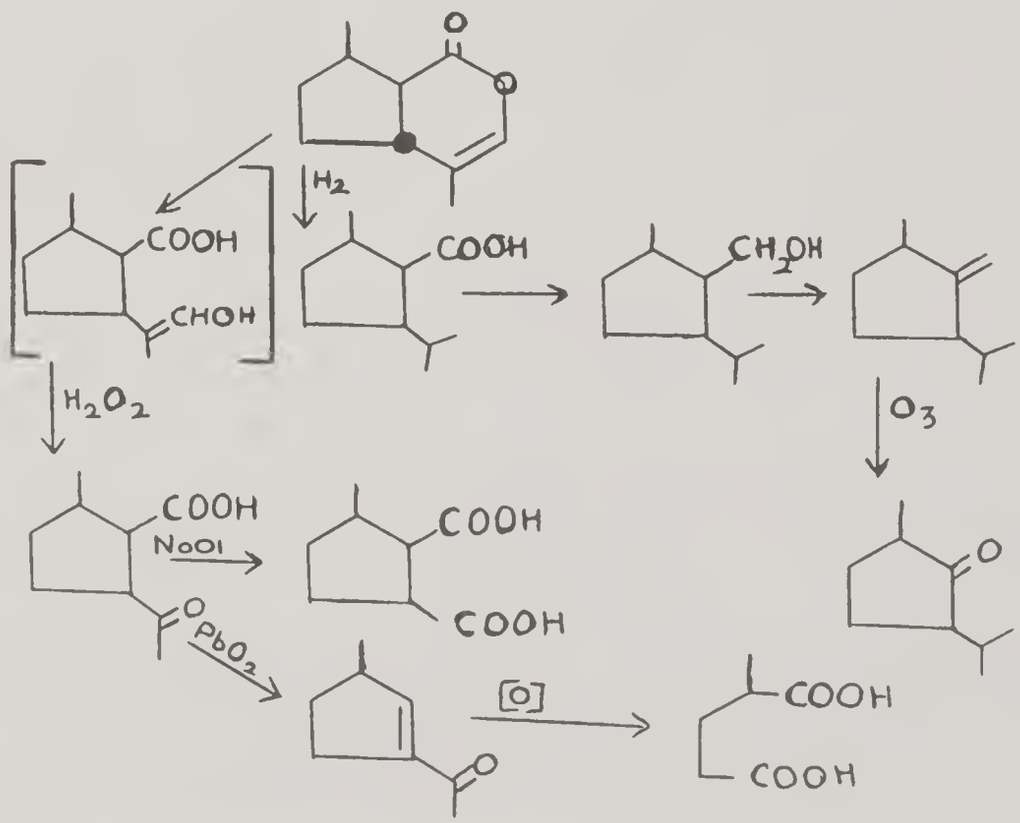
THE CYCLOPENTANE GROUP

1-Acetyl-4-*iso*propylidene*cyclo*pentene (CXXVI) has been isolated from *Eucalyptus globulus*. Hydrogenation and hypobromite oxidation give 3-*iso*propyl*cyclo*pentanecarboxylic acid, whilst sodium and moist ether reduction followed by oxidation gives pinolone (CXXVII).

Nepetalactone (CXXVIII), as was first demonstrated by McElvain, is the active principle of oil of catnip, from *Nepeta cataria*. It is of particular interest, apart from its potent physiological activity, in that it is an enol lactone. Nepetalic acid, its hydrolysis product, exists in the tautomeric forms (CXXIX), (CXXX), and (CXXXI). The structure has been established as shown (47), the results leading to the shown stereochemistry. The oxidative decarboxylation of the γ-keto acid with lead dioxide is of interest as being related to Doering's (48) *bis*decarboxylation of 1 : 2-dicarboxylic acids.


(CXXVI)
O
O
COOH
OH
O
(CXXVII)


(CXXVIII)
O
O
OH
H
(CXXXI)
COOH
CHOH
(CXXIX)
COOH
CHO
(CXXX)


O
O
H2
COOH
CHOH
COOH
CH2OH
H2O2
O3
COOH
NaOI
COOH
COOH
O
PbO2
[O]
COOH
COOH

From various species of ants a number of interesting terpenoids have been isolated. Iridomyrmecin (CXXXII) is typical of these (49) and it has been simply related to nepetalactone by oxidation with permanganate. The resultant dicarboxylic acid (CXXXIII) had been previously obtained from nepetalactone and, being of known stereochemistry, established that of iridomyrmecin.

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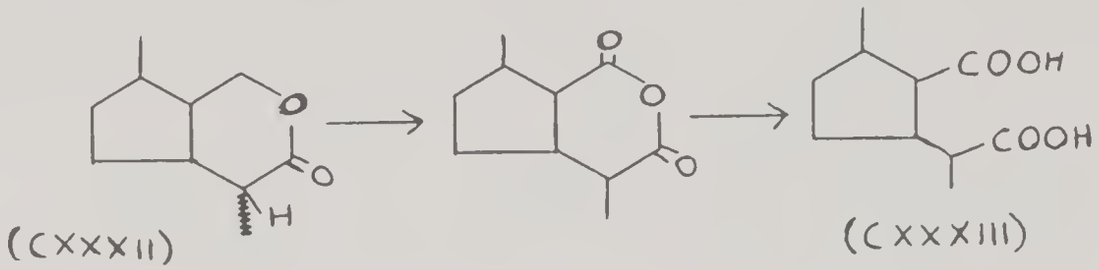

(CXXXII) (CXXXIII)

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THE BICYCLIC MONOTERPENOIDS: I

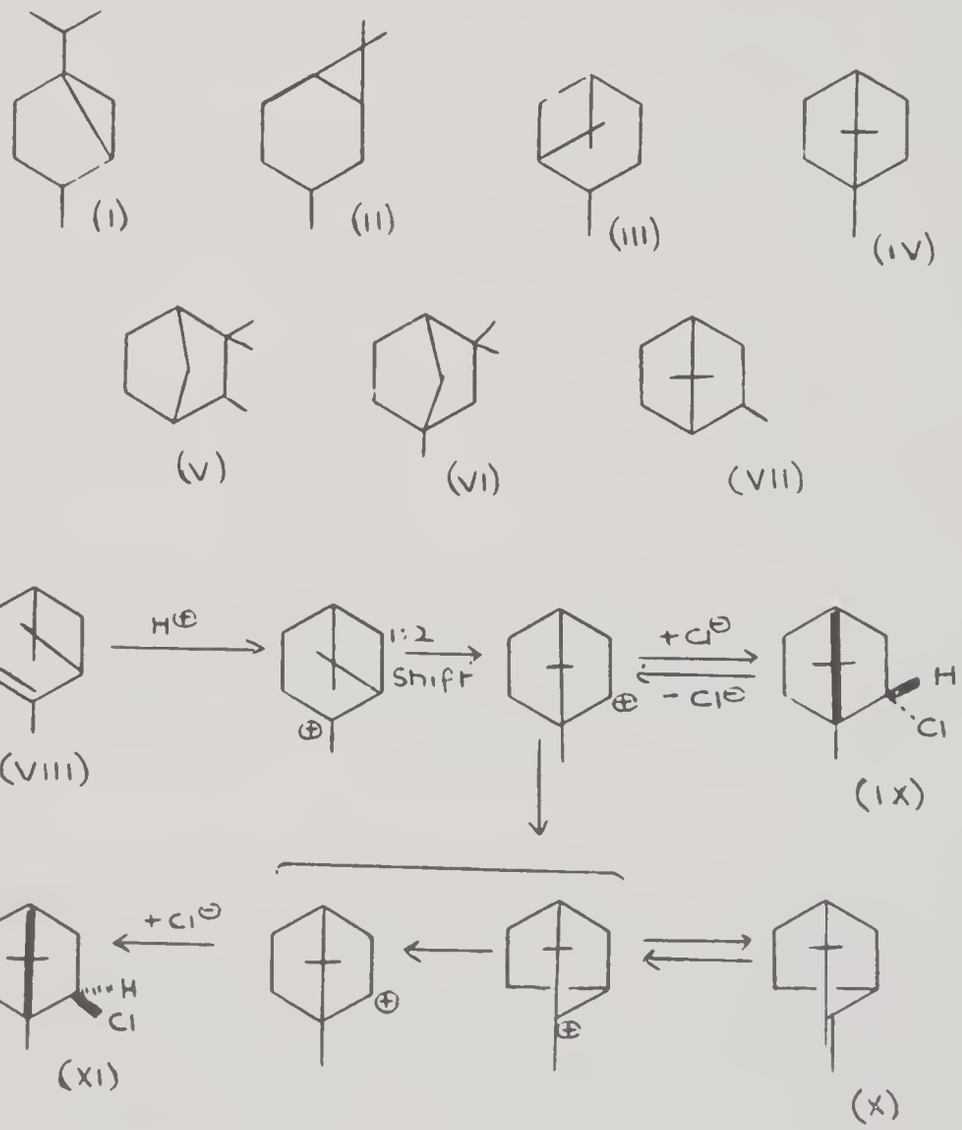
The bicyclic monoterpenoids are the most interesting of the monoterpenoid group because of the profound skeletal transformations they readily undergo. For classification purposes only they may be divided into seven groups, but the groups are somewhat arbitrary since one chemical change can transform a substance of one series into one of another, or even into the monocyclic group; the latter is particularly true of those substances containing a *cyclo*propane ring.

The principal saturated bicyclic monoterpenoid hydrocarbons are thujane (I), carane (II), pinane (III), camphane (IV), *iso*camphane (V), fenchane (VI), and *iso*bornylane (VII).

The transformations mentioned, characteristic of this series, are instances of carbonium ion rearrangements. In this chapter they will be discussed as simple classical carbonium ions; in the following chapter some of the more recent work resulting in the concept of bridged ions and their stereochemical implications will be indicated.

One of the rearrangements so frequent in this series is known as the "Wagner-Meerwein," and for its discussion some of the substances to be mentioned later must be described.

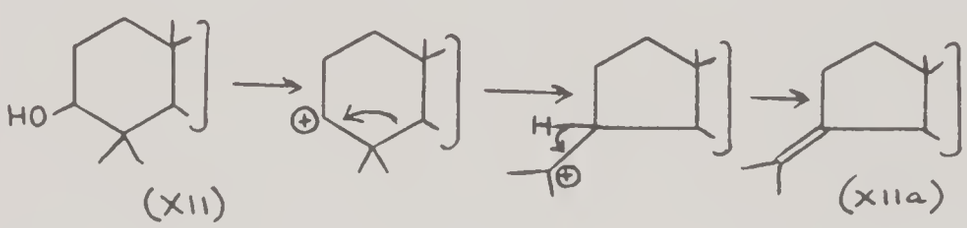
By treatment of α-pinene (VIII) with anhydrous hydrogen chloride (1) a hydrochloride (IX) is obtained, which does not, however, have the same carbon skeleton as its progenitor. On treatment with base it eliminates hydrogen chloride and camphene (X), a member of the *iso*camphane group, is obtained. Furthermore, camphene, on treatment with hydrogen chloride, does not reform the original hydro-


(I)
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)
H⊕
1:2 Shift
+Cl⊖
- Cl⊖
H
Cl
(IX)
+Cl⊖
H
Cl
(XI)
(X)

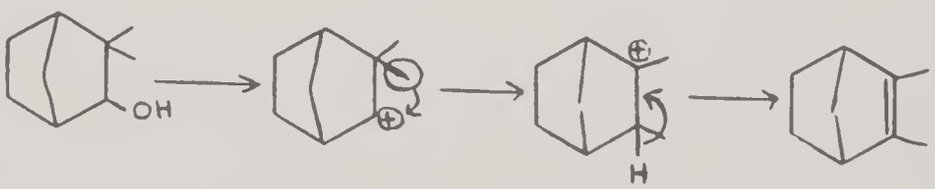
chloride, now known as bornyl chloride (IX), but gives the chloro compound (XI) of a substance of the camphane group. In the cases of both camphene and α-pinene the hydrochlorides corresponding to the original skeleton have been obtained by working under very mild conditions, but both are unstable, rapidly rearranging. This series of reactions can be simply explained as a series of 1:2 shifts of the carbonium ions formed by initial protonation of the double bond in α-pinene. This description is grossly oversimplified in several senses. Firstly, the carbonium ion may not necessarily have an appreciable lifetime and the protonation (or loss of chloride ion) may to some degree be concerted with the 1:2 shift and the subsequent loss of a proton (or addition of chloride ion). Secondly, the various carbonium ions are written in their simplest classical forms, whereas the actual entity involved in the transition state may be a hybrid of which the ions represented are canonical forms or approximate thereto. Thirdly, one ion in equilibrium with derived products may give one product most rapidly (kinetic control) and another, the most stable, slowly (thermodynamic control). Further, this "intermediate" ion may have special properties, particularly of stereochemistry, not immediately apparent in the extreme classical structures. These factors will be considered later (pages 154*ff.*), the classical notation being sufficient to describe much of the behaviour of these substances, though not, immediately, the retention of stereochemical identity during these transformations.

Similar 1:2 ion shifts are found throughout terpenoid chemistry. One such, which is much employed diagnostically in the triterpenoids, involves the partial grouping (XII). When the hydroxyl group is in the correct (equatorial) configuration the transformation (XII) → (XIIa) takes place, if the substance is treated with phosphorus pentachloride.

The shifts so far described involve the movement of electrons constituting part of a ring. In the dehydration of camphenilol depicted opposite, the 1:2 shift is that of a methyl group. This type of rearrangement, which again is very widespread in terpenoid chemistry, is known in monoterpenoid compounds as the Nametkin rearrangement. An interesting example of a Nametkin-type rearrangement is (2) the conversion of (−)-camphor (XIII) to (+)-camphor



(XII) (XIIa)

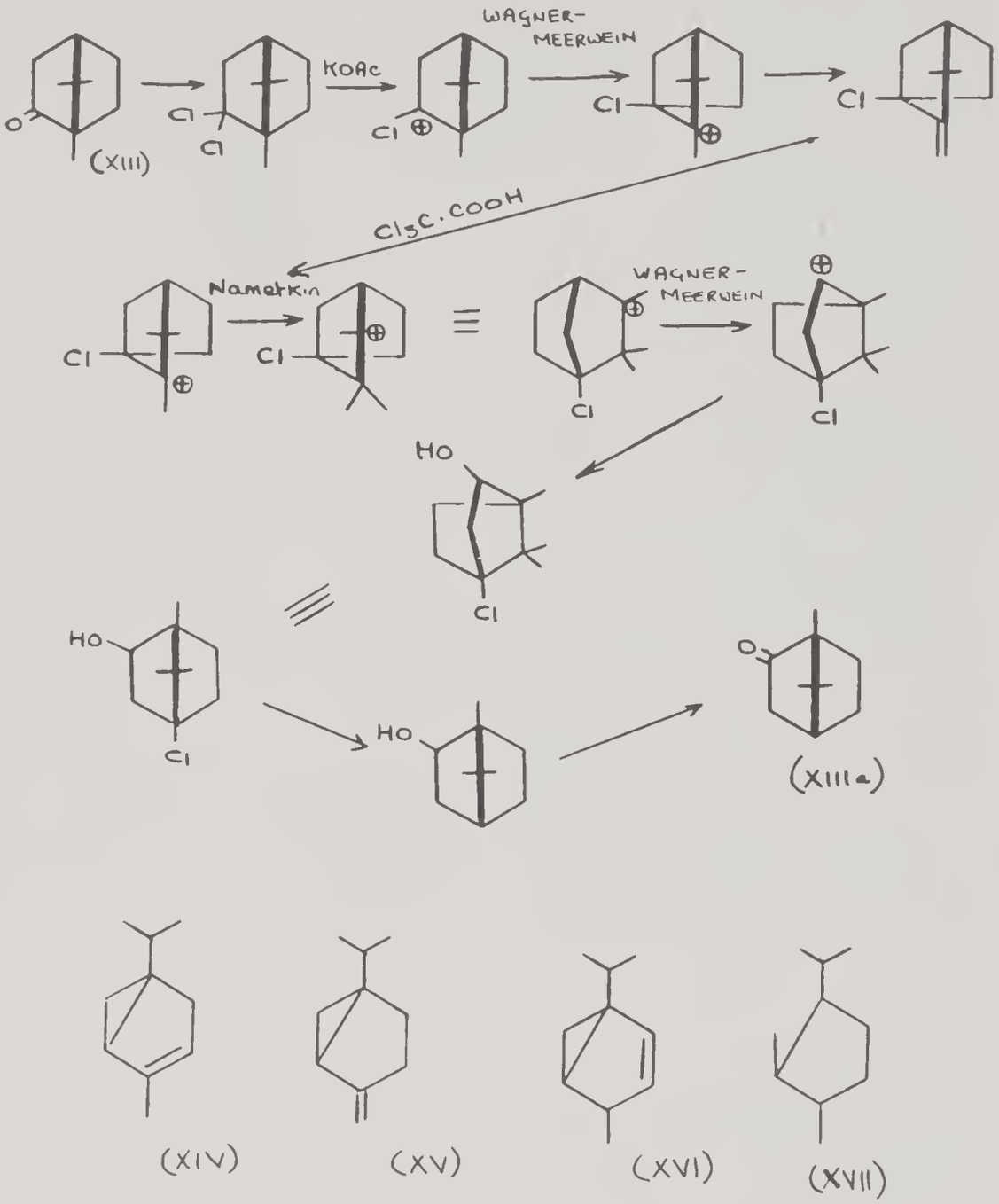


NAMETKIN REARRANGEMENT

(XIIIa). (–)-Camphor with phosphorus pentachloride gives 2:2-dichlorocamphene, the latter losing hydrochloric acid with potassium acetate, and rearranging to give α-chlorocamphene. This, with trichloroacetic acid, undergoes a more complex change to give 4-chloro*iso*borneol, reduced with sodium and alcohol to (–)-*iso*borneol and thence, by oxidation, to (+)-camphor.

THE THUJANE GROUP

The naturally occurring hydrocarbons in this group are α-thujene (XIV) and **sabinene** (XV). The first is found in the turpentine from *Boswellia serrata* Roxb. and in origanum oil, whilst the second is found in oil of savin. α-Thujene may also be obtained by dehydrating, by the xanthate method, one of the isomeric thujyl alcohols. From another isomeric alcohol the hydrocarbon β-thujene (XVI) can be prepared. All three hydrocarbons give thujane on hydrogenation. The *cyclo*propane ring in thujane opens, under the influence of acid, to give *cyclo*pentane derivatives (XVII) in accordance with the Markownikoff rule—that is, the proton attacks the most negative (least substituted) carbon atom, the ring then opening to give the most stable carbonium ion, in this case tertiary, which then either is attacked by the available anion or else loses a proton to introduce a double bond. Exceptions to such Markownikoff addition

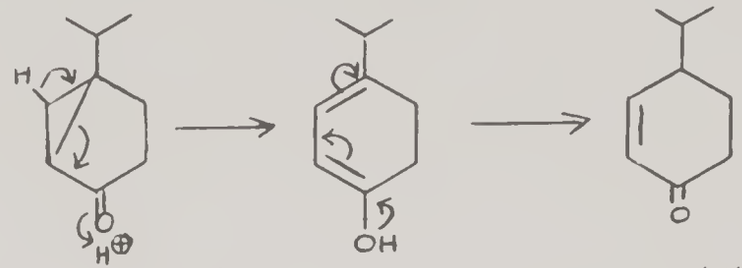


(XIV) (XV) (XVI) (XVII)

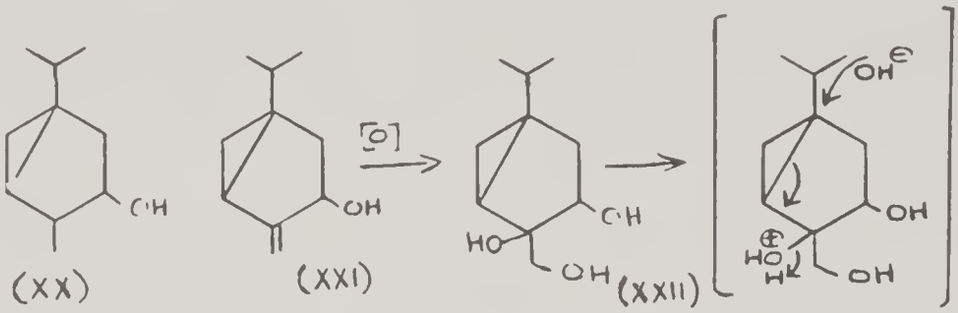
all appear to have special features. Thus, ozonolysis of sabinene affords sabina ketone (XVIII) which is isomerised by acid to (XIX). In this case the oxygen of the carbonyl group is the most basic centre and is attacked by the proton, as shown opposite.

Thujyl alcohol (XX) exists in oil of wormwood as a mixture of isomerides, the stereochemistry of which has been investigated and elucidated (3) by methods similar to those used for the menthols. On oxidation it gives thujone. Sabinol (XXI), from oil of savin, on oxidation with permanganate gives the triol (XXII). With acid this does not open to a *cyclo*pentane but gives cumin alcohol (XXIII): Again the apparent deviation from Markownikoff cleavage results from attack at the most basic centre, in this case the tertiary hydroxyl. Support for this view is found in the fact that an unsaturated triol (probably XXIV) may be isolated as an intermediate.

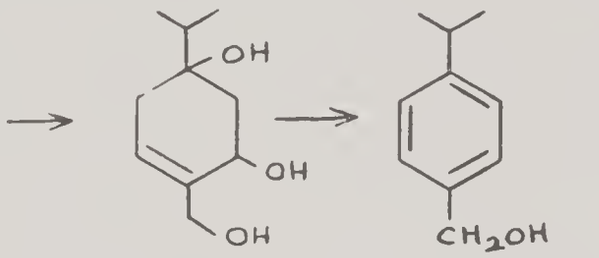
Thujone (XXV) occurs in a number of essential oils, such as those of tansy and thuja. On oxidation with permanganate it is converted into α-thujaketonic acid (XXVI), the latter with hypobromite giving α-thujadicarboxylic acid (XXVII). After esterification this, on treatment with methoxide ion, undergoes an interesting reaction to give tanacetophorone (XXVIII). This process has been formulated as shown opposite, though a preliminary cleavage followed by a Dieckmann would not seem to be excluded (4). By distillation under



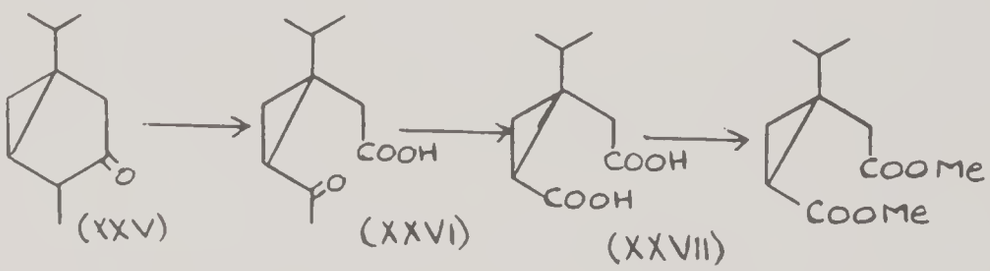
(XVIII) (XIX)



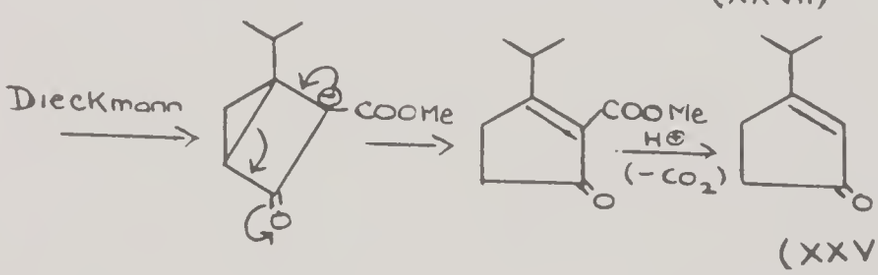
(XX) (XXI) (XXII)



(XXIV) (XXIII)



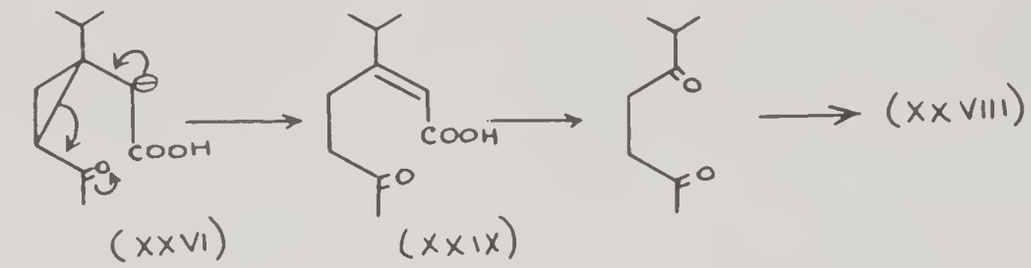
(XXV) (XXVI) (XXVII)



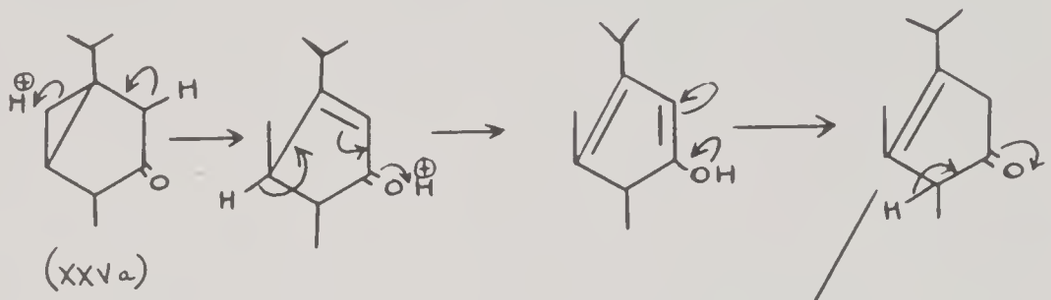
(XXVIII)

reduced pressure, or by heating with water, α-thujaketonic acid is isomerised to β-thujaketonic acid (XXIX) which is oxidised by permanganate to the diketone. Base cyclisation then gives (XXVIII). The latter is also obtained by pyrolysis of the calcium salt of (XXIX), and its constitution has been shown by oxidation to ω:ω-dimethyllevulic acid.

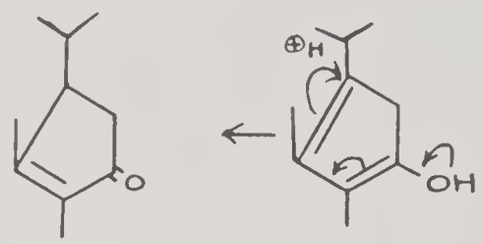
When thujone is dissolved in cold concentrated sulphuric acid it is isomerised, possibly as indicated (XXVa), etc., to give isothujone (XXX) (5). The structure of this substance has been shown by oxidative degradation, the first product being a keto-lactone (XXXI), which can be further degraded to *iso*propylsuccinic acid. Since the



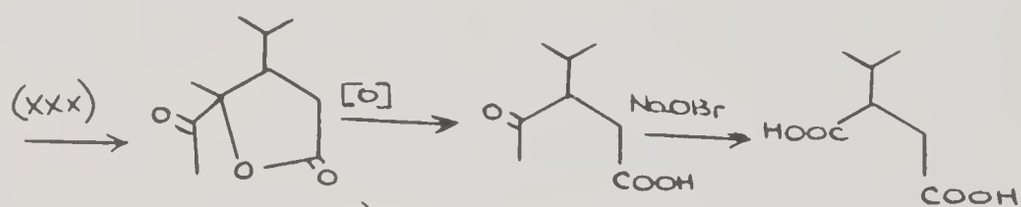
(XXVI) (XXIX)



(XXVa)



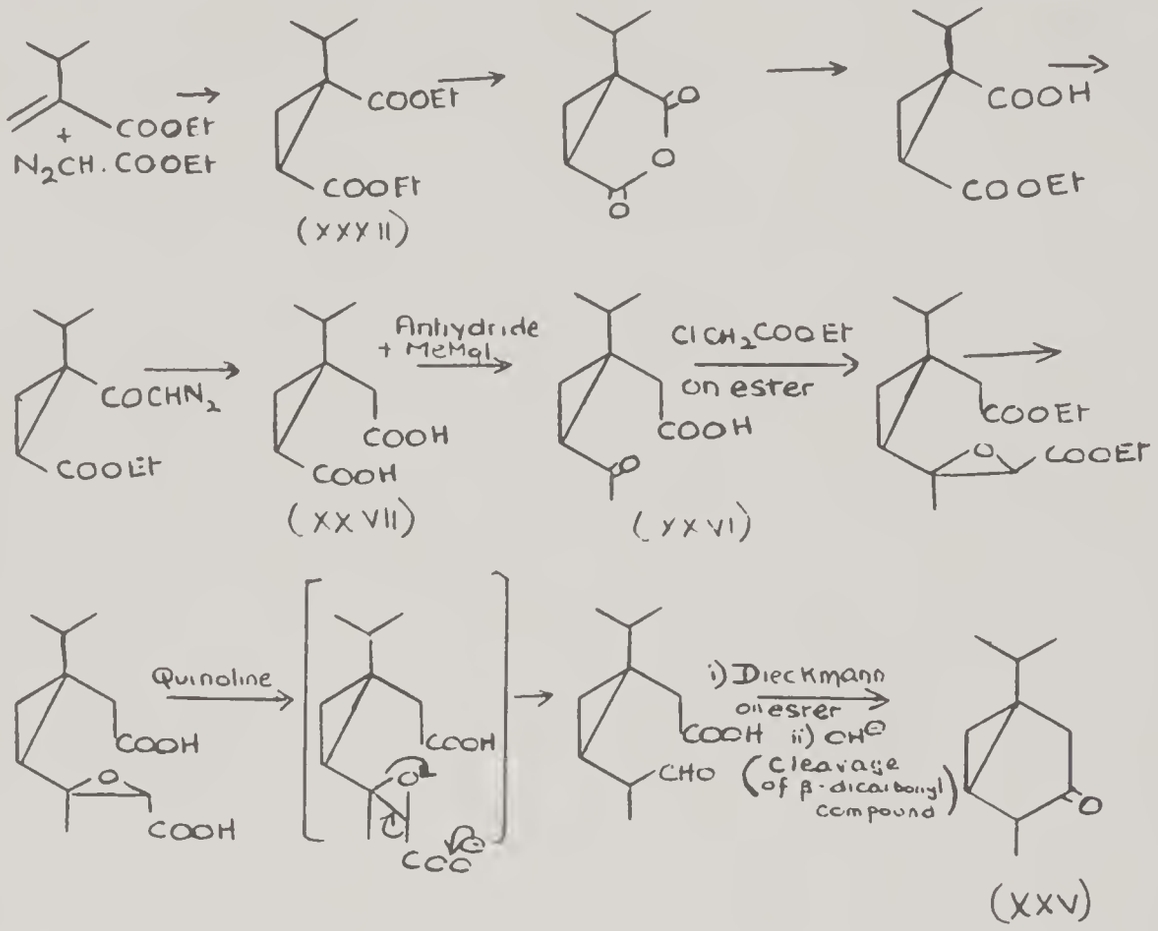
(XXX)

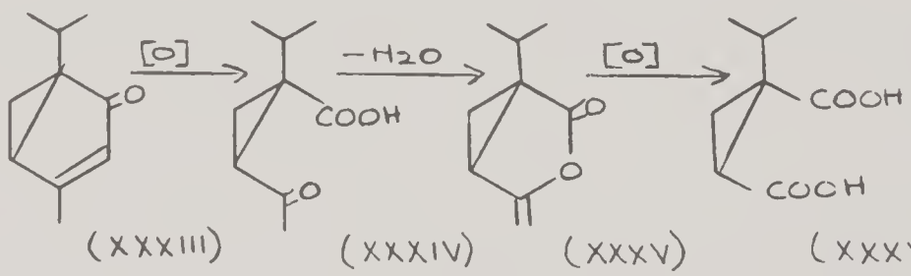


(XXXI)

diester of umbellularic acid (XXXII) has been synthesised (6) and converted (7) into both thujadicarboxylic acid (XXVII) and α-thujaketonic acid (XXVI), the conversion of the latter (8) to thujone constitutes a total synthesis.

Umbellulone (XXXIII) occurs in the essential oil from the leaves of *Umbellularia californica* Nuttal. It was shown to be an α:β-unsaturated ketone because with hydroxylamine and with semicarbazide it gave a hydroxylamino oxime and a semicarbazido semicarbazone, respectively, both products of β addition to the conjugated double bond. Permanganate oxidation of umbellulone resulted in cleavage at the double bond with the loss of one carbon atom to give umbellularic acid (XXXIV) which still contained a carbonyl group, as shown by oxime formation. Distillation resulted in loss of water and the formation of the enol lactone (XXXV), further oxidised by permanganate to *cis*-umbellularic acid (XXXVI) (cf. XXXII). (XXXVI) is very stable to acid despite the presence of the *cyclo*propane ring, presumably because of the strong deactivation by the two carboxyl groups and resistance to the formation of a primary carbonium ion. The bromination products of umbellulone are of particular interest (9). When the crude product obtained by treating umbellulone with bromine in carbon tetrachloride is distilled, hydrogen bromide is evolved and umbellulone dibromide is a major product. It is resistant to further bromination and to the attack of silver ion. Its ultra-violet spectrum ($\lambda_{max.}$ 250 mμ) indicates conjugation. With zinc in acetic acid, however, it is partially reduced to give bromodihydroumbellulone (XLII), which has similar properties to the dibromide. Reduction of the dibromide in alkali with

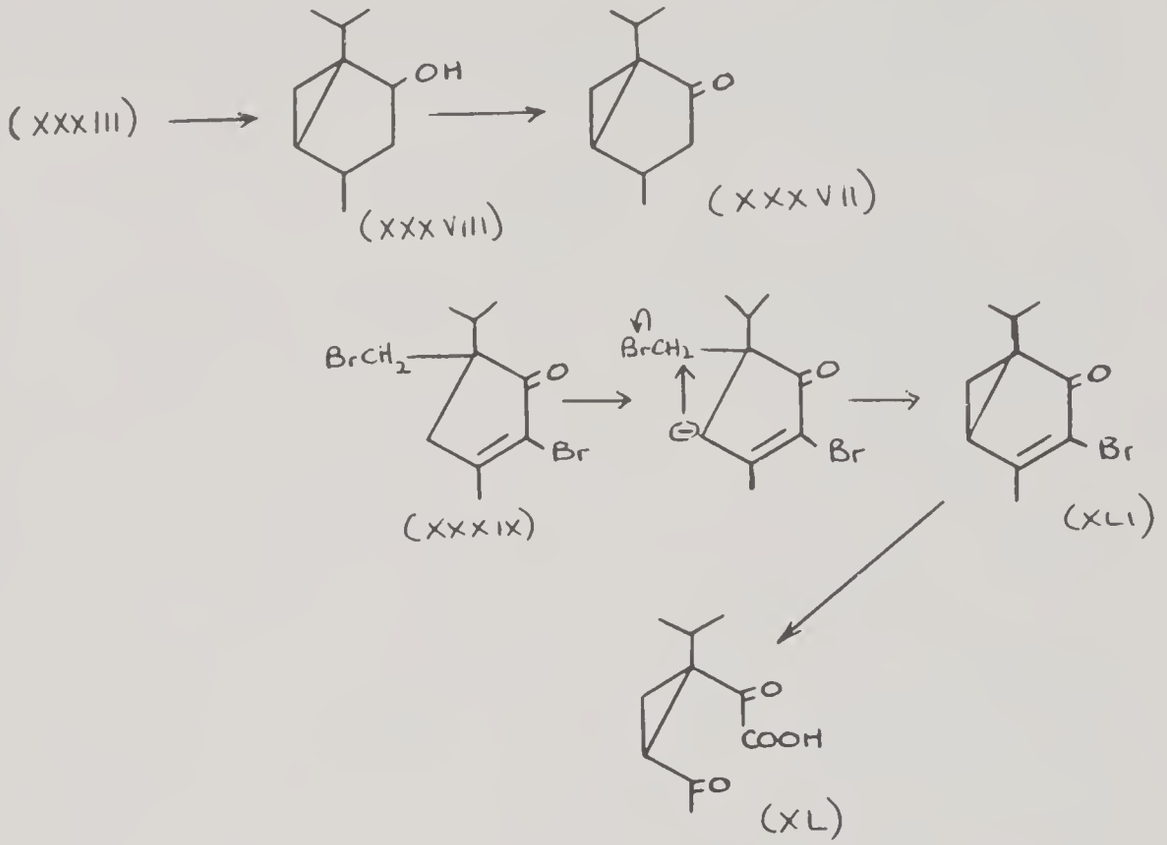

COOEt
+
$N_2CH.COOEt$
COOEt
COOEt
(XXXII)
COOH
COOEt
$COCHN_2$
COOEt
Antiydride
+ MeMgI
COOH
COOH
(XXVII)
$ClCH_2COOEt$
on ester
COOH
(XXVI)
COOEt
COOEt
Quinoline
COOH
COOH
COOH
i) Dieckmann
on ester
ii) $OH^{\ominus}$
CHO
(Cleavage
of β-dicarbonyl
compound)
(XXV)

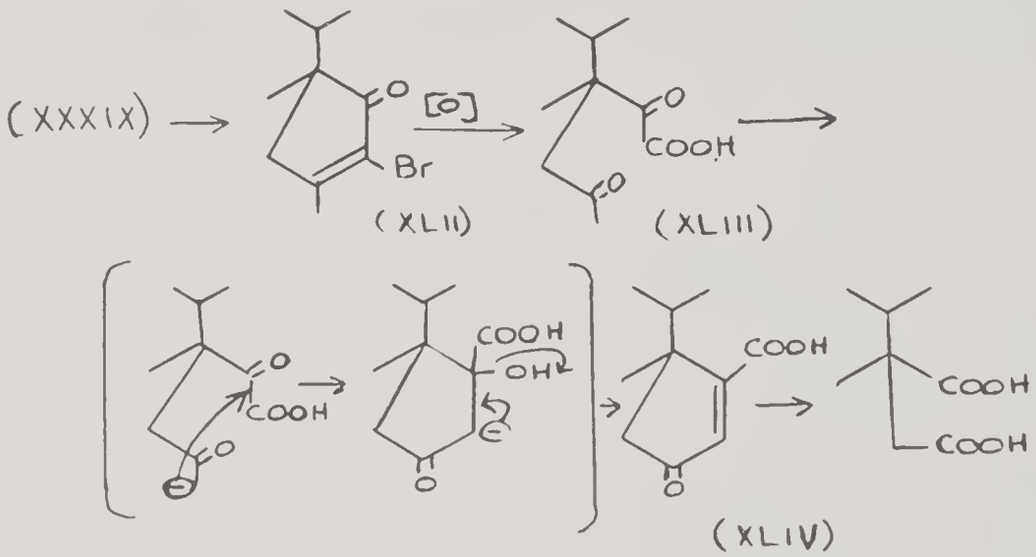

[O]
$-H_2O$
[O]
COOH
COOH
(XXXIII)
(XXXIV)
(XXXV)
(XXXVI)

Raney nickel gives β-dihydroumbellulone (XXXVII), also obtained by the reduction of umbellulone with sodium and alcohol to (XXXVIII) followed by chromic acid oxidation.

These reactions are explained by the formula (XXXIX) for dibromoumbellulone. The resistance to dehydrobromination is explained in one case because it is a neopentyl bromide and in the other because it is a vinylic bromide. On oxidation with permanganate in bicarbonate it gives (XL) by the mechanism shown, whilst fuming nitric acid is said to oxidise the methyl group to carboxyl. Both (XXXVII) and (XL) are derived through (XLI), which is itself obtained by the action of potassium acetate on (XXXIX), being produced by anionic internal attack on the neopentyl bromide. This parallels the formation of carenone (page 84). On this interpretation bromodihydroumbellulone is represented as (XLII) and this has been confirmed by degradation with permanganate to the diketo acid (XLIII). This, with strong base, undergoes the aldol condensation to (XLIV). Vigorous oxidation of this with permanganate followed by nitric acid gave α-methyl-α-*iso*propylsuccinic acid.

Whilst these experiments are compelling as regards the structure of umbellulone dibromide its genesis is not entirely clear. The


(XXXIII)
OH
(XXXVIII)
O
(XXXVII)
BrCH2
O
Br
(XXXIX)
BrCH2
O
Br
O
Br
(XLI)
O
COOH
O
(XL)

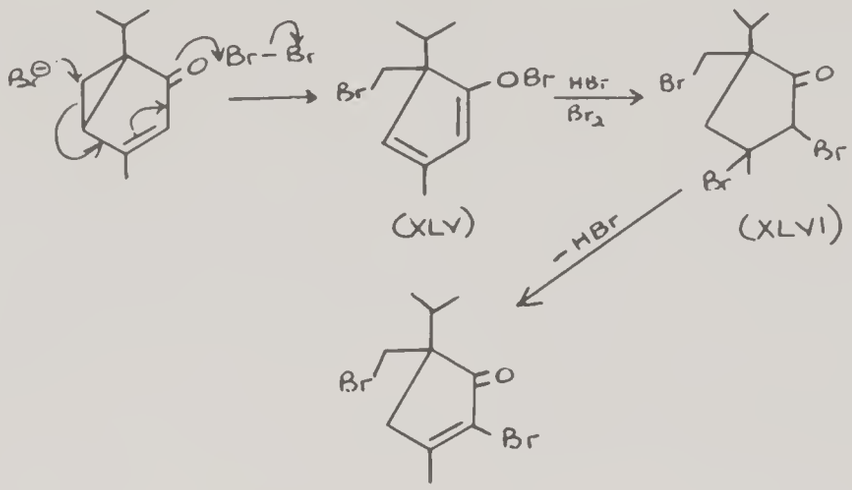

(XXXIX)
O
[O]
Br
(XLII)
O
COOH
O
(XLIII)
O
COOH
COOH
OH
O
COOH
COOH
COOH
(XLIV)

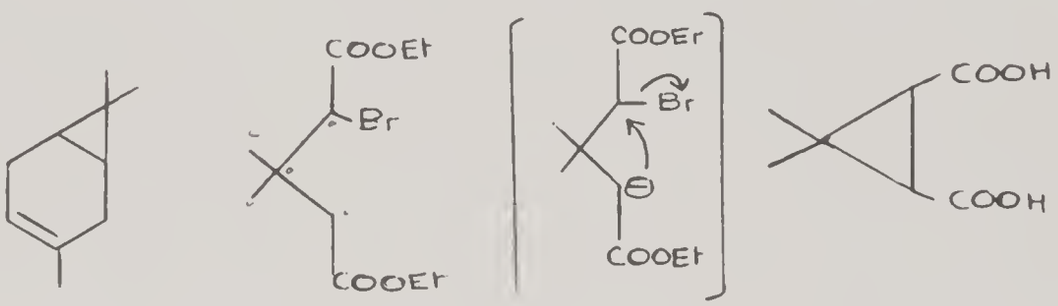
first stage is probably addition of bromine to give the bromide (XLV) with concomitant cleavage of the *cyclo*propane ring. Further attack by bromine then gives (XLVI).

THE CARANE GROUP*

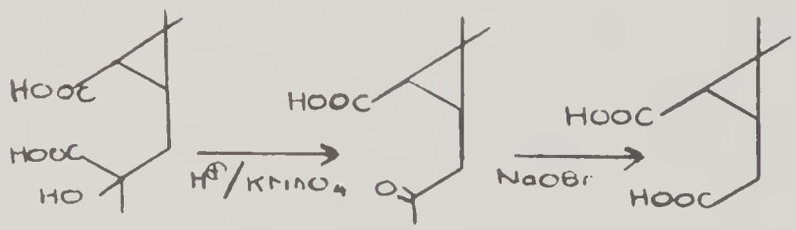
The hydrocarbon car-1(6)-ene (XLVIII) is a constituent of a number of turpentine oils and is now recognised to be the precursor of the hydrocarbon sylvestrene. It occurs largely in the (+) form, but the (−) antipode has also been detected. Its structure was elucidated largely by oxidative degradation. A number of products were obtained of which the most complex were hydroxy acids of the formula $C_{10}H_{16}O_5$. Together with these were found dimethyl-malonic acid, *cis*-dimethylsuccinic acid and both *cis*- and *trans*-caronic acids (XLIX). The identification of the latter two acids, which had already been synthesised (10), indicated the presence of a *cyclo*propane ring in the molecule. The position of the double bond in carene was shown essentially by the further stepwise degradation of the C_{10} hydroxy acids to homocaronic acid (LI). The latter has been synthesised. Treatment of (XLVIII) with hydrogen chloride gives dipentene hydrochloride (LII) and sylvestrene hydrochloride (LIII) by opening of the *cyclo*propane ring in both directions.

*The numbering used here is consistent with that of the *p*-menthane system from which it is derived. Other numberings have, however, been used.

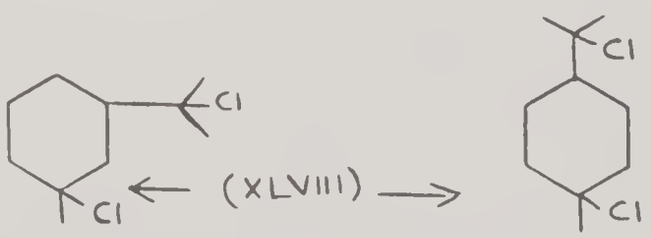




(XLVIII) (XLIX)



(L) (LI)



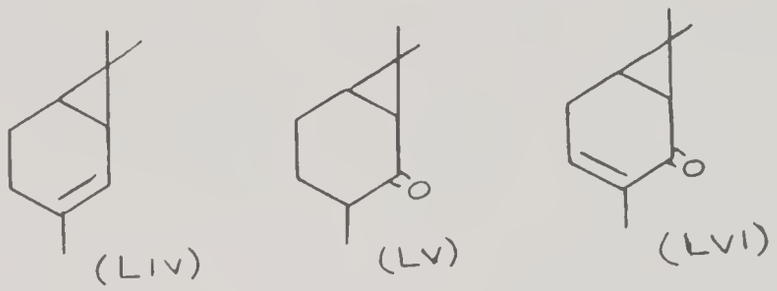
(LIII) (LII)

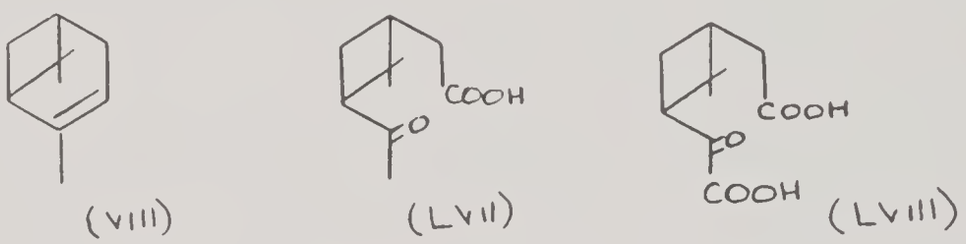
(+)-Car-1-ene (LIV) was first isolated from *Andropogon jwarancusa* Jones, but has since been found in other essential oils. Its structure was established by oxidative degradations similar to those applied to its isomer. The ketone (carone) (LV) does not occur naturally but has been prepared from dihydrocarvone hydrobromide (page 82). The structure (LVI) of an unsaturated carone was for a long time not believed to refer to an isolable compound, since attempts to prepare it gave the monocyclic seven-membered eucarvone. Very recently, as already mentioned, its existence under mild conditions has been clearly demonstrated (see page 84).

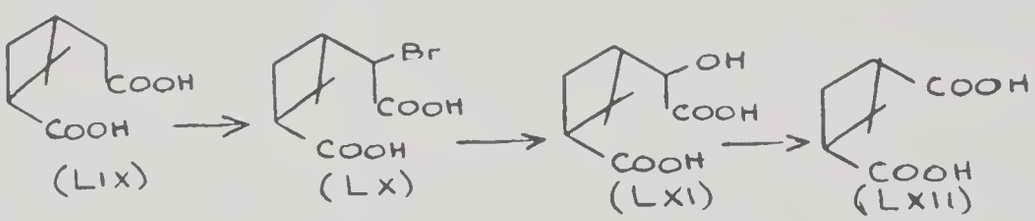
THE PINANE GROUP

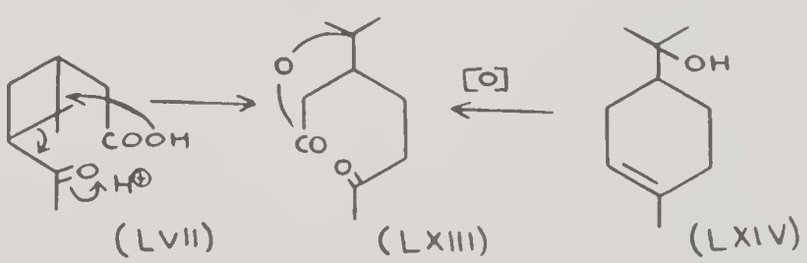
The most important member of this group, and the most investigated, is the hydrocarbon **α-pinene** (VIII). Its structure was determined (with elucidation of its then extraordinary feature, the four-membered ring) by a series of oxidations of which only a slight indication can be given. α-Pinene is very widely distributed in nature and is present in the oils derived from most conifers; it is the chief constituent of turpentine, a substance which has been known for several centuries.

Its investigation was undertaken at the beginning of the nineteenth century and its correct analysis was recorded in 1818. At about the same time Biot made the discovery that French oil of turpentine was optically active, an observation that was to lead to Pasteur's discoveries and thence to the theories of Le Bel and Van't Hoff. The oxidation of α-pinene (VIII) was studied by, amongst others, Baeyer who showed that with permanganate two main products were obtained: pinonic acid (LVII) and pinoylformic acid (LVIII). The former, with hypobromite, gave a dicarboxylic acid, pinic acid (LIX), brominated to (LX) and converted to the hydroxydicarboxylic acid (LXI) with barium hydroxide. Lead dioxide then cleaved the α-hydroxy acid to give *cis*-norpinic acid (LXII) which was extremely stable. Baeyer further found that with mineral acid (LVII) was attacked to give homoterpenyl methyl ketone (LXIII), a compound previously obtained from α-terpineol (LXIV). The structure of norpinic acid was confirmed many years later by syn-


(LIV)
(LV)
(LVI)

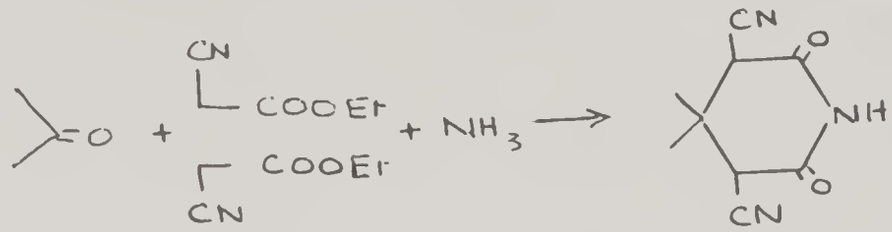

(VIII)
COOH
(LVII)
COOH
COOH
(LVIII)

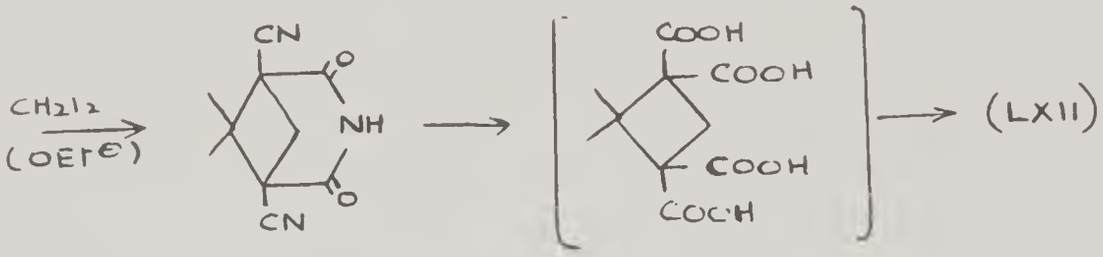

COOH
COOH
(LIX)
Br
COOH
COOH
(LX)
OH
COOH
COOH
(LXI)
COOH
COOH
(LXII)

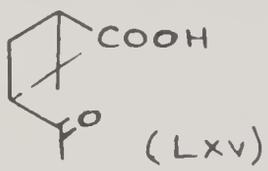

COOH
(LVII)
(LXIII)
[O]
OH
(LXIV)

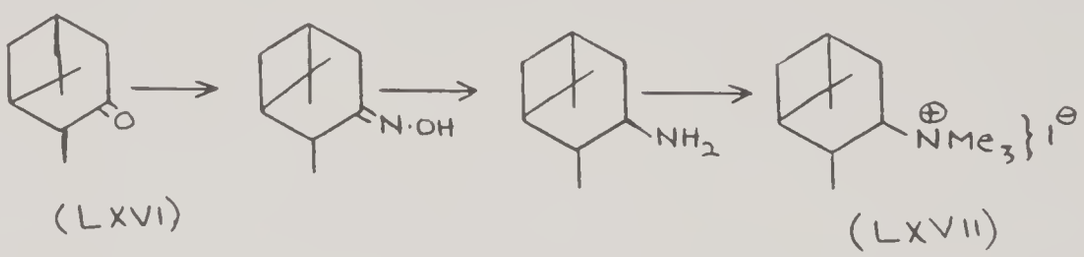
thesis (12) in the following way. Two molecules of cyanacetic ester were condensed onto one molecule of acetone with ammonia to give a cyclic imide. Base-catalysed alkylation with methylene diiodide constructed the *cyclo*butane ring; hydrolysis and decarboxylation of the intermediate malonic acid then gave *trans*-norpinic acid. By conversion into *cis*-norpinic anhydride it may be isomerised to the *cis* acid. *cis*-Norpinic anhydride has been converted into pinononic acid (LXV) (13). Although no direct synthesis of α-pinene has been recorded, the summation of a number of syntheses by different workers leads from norpinic acid to the hydrocarbon. The last stage is the conversion from pinocamphone (LXVI) (page 124) (14), a naturally occurring ketone, to the quaternary base (LXVII) which, on Hofmann degradation, gave a mixture of α-pinene and an isomer (LXVIII) δ-pinene. The α-pinene was isolated as the nitrosochloride, the presence of the isomer in the mixture being demonstrated by oxidation and isolation of pinocamphoric acid (LXIX).

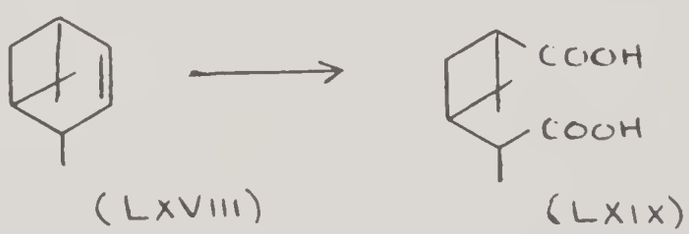
This structure of α-pinene, first suggested by Wagner (15), is therefore entirely secure. However, investigation by other authors, in particular Tiemann and Semmler, revealed apparent discrepancies. Using chromic acid as the oxidising agent, they isolated in the


CN
COOEt
COOEt
CN
+ NH3
O
NH
O
CN


CH2I2
(OEt⊖)
CN
O
NH
O
CN
COOH
COOH
COOH
COOH
(LXII)


COOH
O
(LXV)

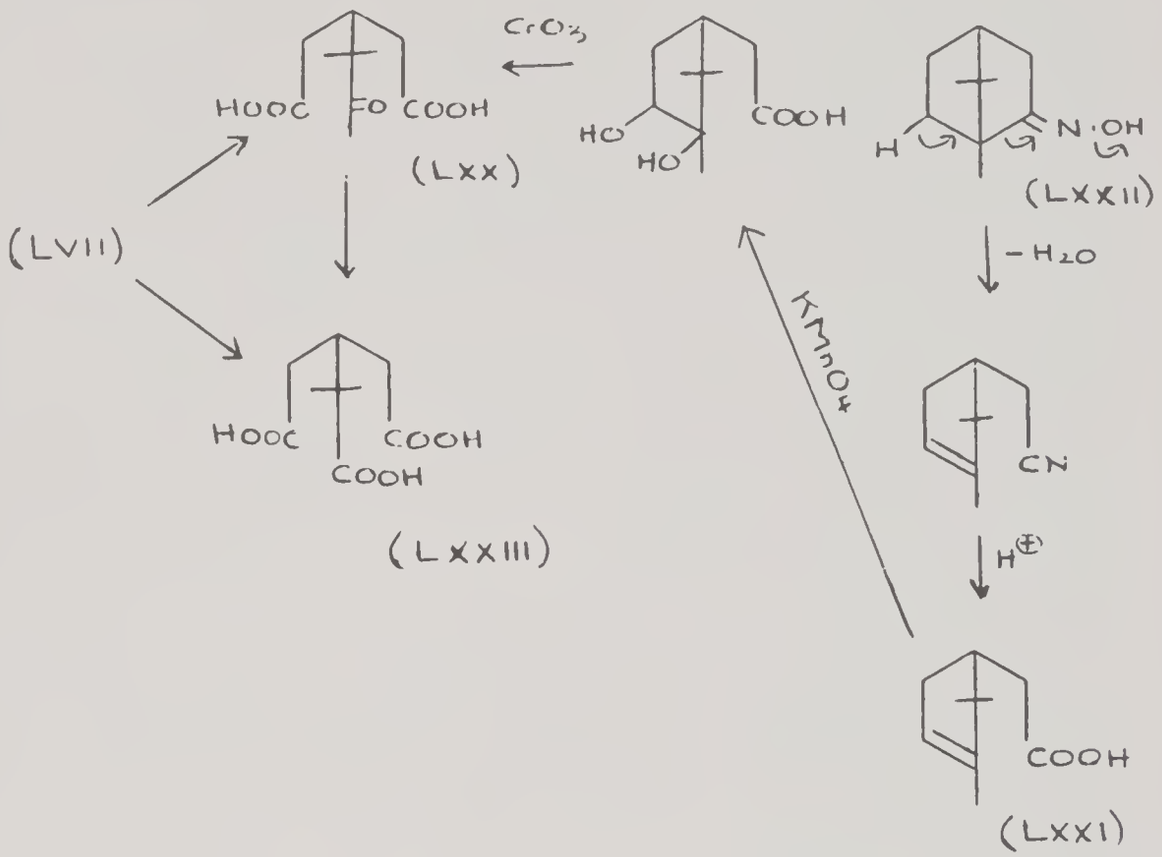

O
N·OH
NH2
⊕NMe3} I⊖
(LXVI)
(LXVII)

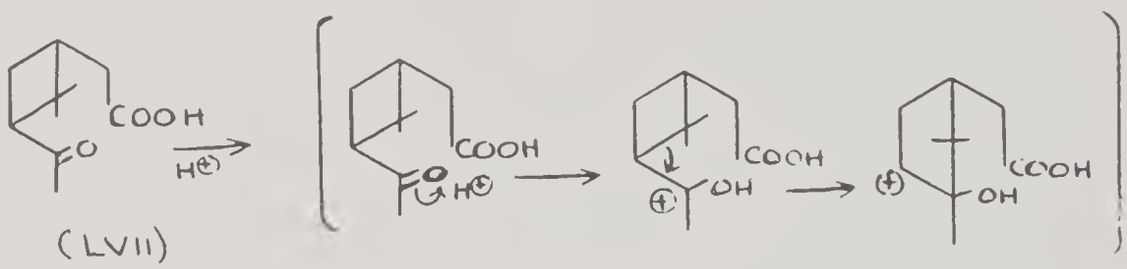

COOH
COOH
(LXVIII)
(LXIX)

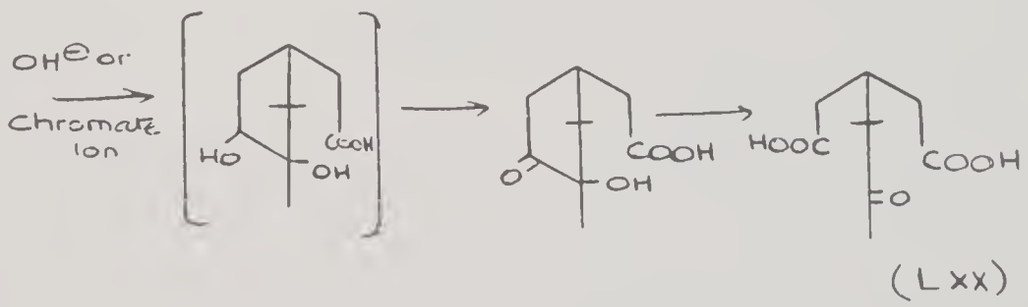
degradation of pinonic acid (LVII), apart from terebic acid, *iso*-ketocamphoric acid (LXX), a substance previously obtained by the oxidation of α-campholenic acid (LXXI), and a tricarboxylic acid, *iso*camphoronic acid (LXXIII). The latter was also obtained from (LXX) by oxidation with hypobromite. α-Campholenic acid is obtained from camphor oxime (LXXII) by acid-catalysed dehydration followed by hydrolysis and so, in the scheme shown opposite, α-pinene would appear to have a camphene skeleton. Added to this the authenticity of the structure (LXXIII) for *iso*camphoronic acid was demonstrated by direct synthesis by Perkin.

Since the structure of α-pinene is established, the only conclusion remaining is that a skeletal rearrangement takes place during the acidic conditions of the chromic acid oxidation which does not occur with permanganate. This may be represented as shown opposite.

The acid treatment of α-pinene gives a large number of products and has been the subject of many investigations (16). Thus, in one series dipentene, terpinolene, and α-terpinene were amongst the products. It will be noted that hydration of the intermediate ion


CrO3
HOOC
O
COOH
(LXX)
HO
HO
COOH
H
N·OH
(LXXII)
(LVII)
-H2O
KMnO4
HOOC
COOH
COOH
(LXXIII)
CN
H⊕
COOH
(LXXI)


COOH
O
H⊕
(LVII)
COOH
O
H⊕
COOH
OH
COOH
OH

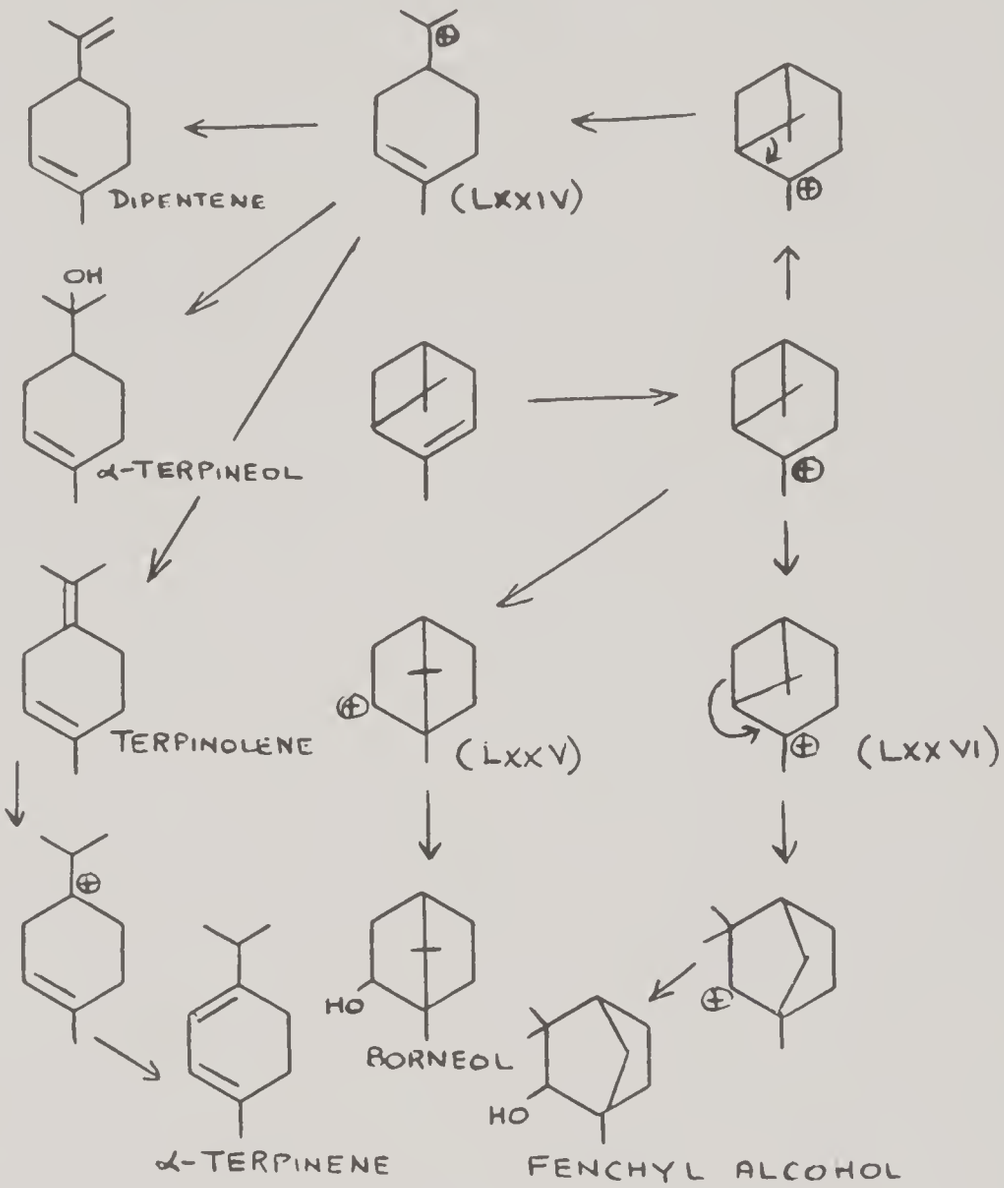

OH⊖ or
Chromate ion
HO
COOH
OH
COOH
O
OH
HOOC
COOH
O
(LXX)

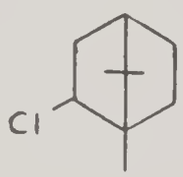
(LXXIV) could produce the corresponding alcohols. α-Terpineol has, indeed, been found and it is conveniently obtained by the action of benzenesulphonic acid on α-pinene. Organic acids have also been used, the products then being the derived esters. Using anhydrous formic acid, however, aside from the above-named substances, bornyl formate is also obtained through the ion (LXXV). Even this does not exhaust the list of substances obtainable by acidic treatment. When a mixture of acetic and sulphuric acids is employed, fenchyl alcohol is amongst the products; the corresponding chloride is also formed to a certain extent by the action of hydrogen chloride on α-pinene at room temperature. These must be presumed formed through the ion (LXXVI) or its equivalent. These varied and interesting reactions may be represented in the scheme shown opposite.

The reaction of α-pinene with hydrogen chloride (page 98) has been very thoroughly investigated and gives, as main product, bornyl chloride (IX). True pinene hydrochloride (LXXVII) has been prepared by the action of hydrogen chloride on pinene under particularly mild conditions: light petroleum solution at -70°. The crystalline hydrochloride is stable in ethereal solution for several days, but reverts eventually to bornyl chloride.

In the above reactions leading to rearrangement or to cleavage, the presence of a double bond (actual or potential) is a prerequisite. Protonation of a double bond to give a carbonium ion, which can then rearrange, is energetically far more favoured than the direct rupture of a four-membered ring; pinane, for instance, is stable to dilute acids. The four-membered ring has therefore a greater stability than has the three-membered which is easily ruptured by acids and by halogens.

The thermal isomerisation of α-pinene is somewhat complex. Under vigorous conditions such exotic products as methylanthracene and phenanthrene are obtained, but under more controlled conditions more closely related substances are obtained. Dipentene and *allo*ocimene constitute much of the material and the latter may be obtained in up to 50% yield. Cyclisation of *allo*ocimene leads


DIPENTENE
(LXXIV)
OH
α-TERPINEOL
TERPINOLENE
(LXXV)
(LXXVI)
HO
BORNEOL
HO
α-TERPINENE
FENCHYL ALCOHOL


Cl

(IX)

Cl

(LXXVII)

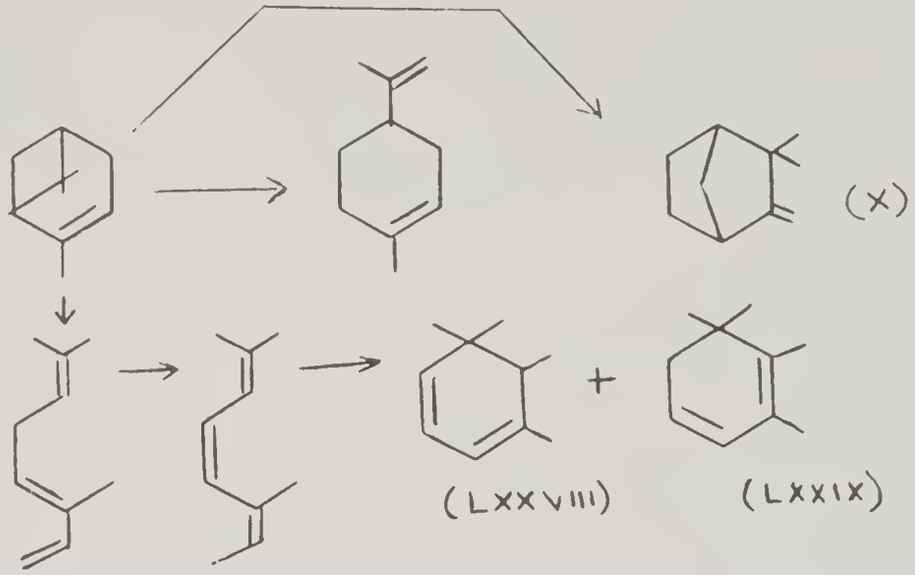
to α- (LXXVIII) and β- (LXXIX) pyronene (17). The rearrangement of α-pinene over certain catalysts gives camphene (X) in high yield; certain patents record over 70% yield. The oxidation of camphene yields camphor.

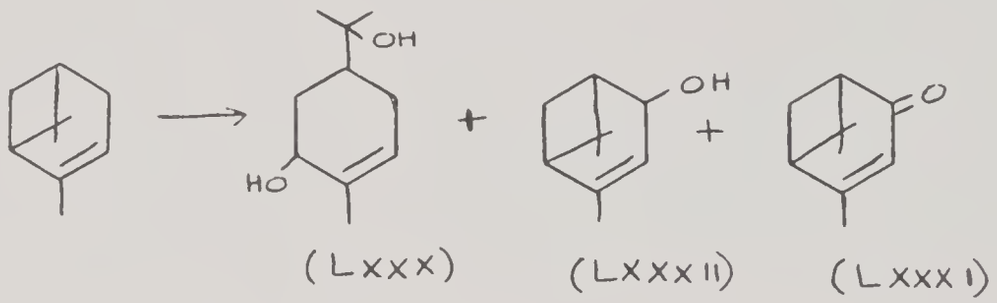
The autoxidation of α-pinene in the absence of water is not of great interest, but in the presence of water and of sunlight the alcohol sobrerol (LXXX) has been isolated. Other products obtained include verbenone (LXXXI) and the corresponding alcohol (LXXXII). The formation of the latter two compounds is not unexpected since autoxidation commonly takes place not on a double bond but at a position α to it. The genesis of optically inactive sobrerol, involving as it does oxidative cleavage of the *cyclo*butane ring, is remarkable. The ruptured bond, allylic, is, however, weaker than the others and is heavily substituted. It is interesting that sobrerol is also formed by the action of aqueous mercuric acetate on α-pinene; it is further transformed by the same reagent into the derived ketone, also obtained with chromic acid.

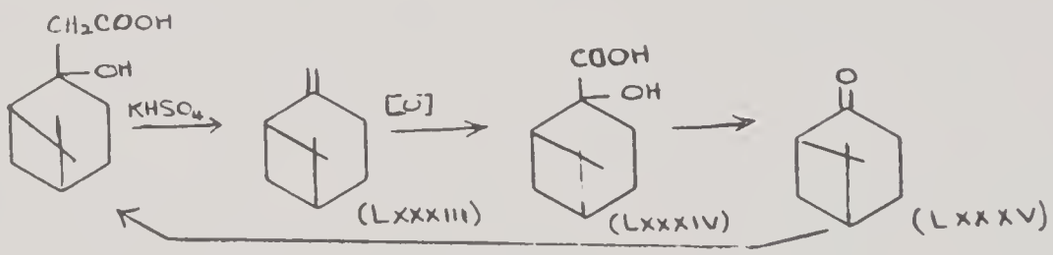
The industrial importance of α-pinene lies in its conversion to α-terpineol—used for the commercial manufacture of perfume—and to bornyl derivatives and camphene for the production of camphor. (−)-β-Pinene (nopinene) (LXXXIII) occurs with α-pinene in varying proportions. (+)-β-Pinene is much rarer; its presence has been shown in the oil from *Ferula galbaniflua*. β-Pinene gives no crystalline derivatives and its presence was inferred by Baeyer (18) when he obtained, during the oxidation of turpentine with permanganate, a small quantity of an acid, nopinic acid (LXXXIV) not formed when pure α-pinene was oxidised. By treatment with lead dioxide this acid gave nopinone (LXXXV) and was therefore an α-hydroxy acid. Nopinone itself was reconverted to β-pinene by Wallach, as shown (19).

These reactions do not, in themselves, prove the presence of a *cyclo*butane ring nor does the vigorous nitric acid oxidation to homoterpenylic acid; however, hydrogenation gives α-pinane identical with the product obtained from α-pinene, and this is conclusive evidence.

In ionic reactions, initiated by protonation, the products obtained from β-pinene are, as would be expected, essentially the

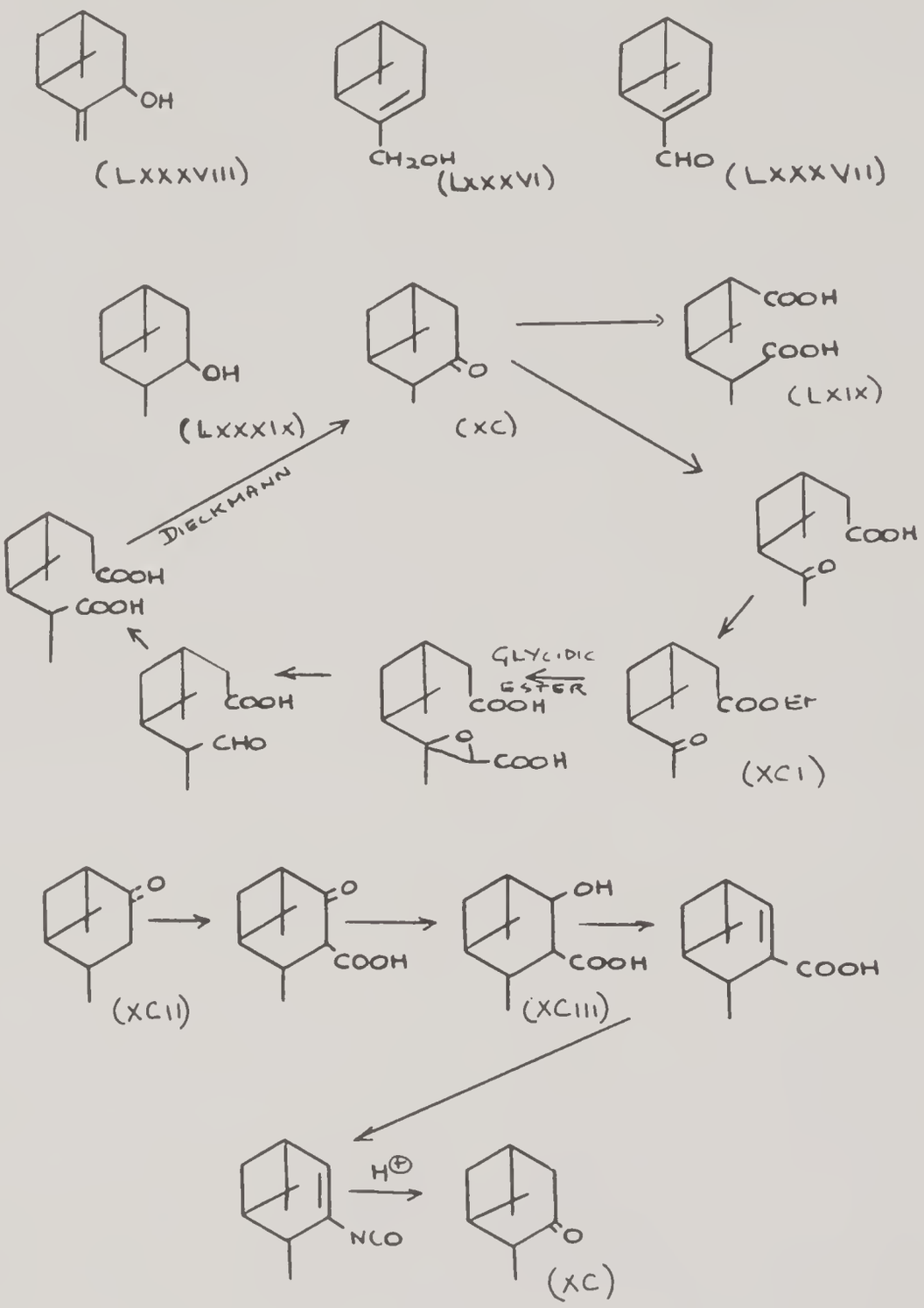

(X)
(LXXVIII)
(LXXIX)


OH
HO
OH
O
(LXXX)
(LXXXII)
(LXXXI)


CH2COOH
OH
KHSO4
[O]
COOH
OH
O
(LXXXIII)
(LXXXIV)
(LXXXV)

same as those from α-pinene. The thermal isomerisation is, however, different and gives myrcene in 70% yield; no *allo*-ocimene is obtained (20). Autoxidation in the presence of catalysts, again α to the ethylenic linkage, gives pinocarveol (LXXXVIII) together with, by allylic rearrangement, myrtenol (LXXXVI) and myrtenal (LXXXVII).

(–)-Pinocampheol (LXXXIX) occurs in oil of hyssop. The related ketone (XC) is also found in this oil to the extent of 45%. The constitution of the ketone was demonstrated by oxidation to a mixture of pinonic and pinocamphoric acids (LXIX) and by partial synthesis from ethyl pinonate (XCI). It has also been synthesised from verbanone (XCII) (21). This was carboxylated with sodamide and carbon dioxide, reduced electrolytically to the hydroxy acid (XCIII), dehydrated, and the carboxyl group reacted with sodium azide which, with Curtius rearrangement and hydrolysis, gave (XC). Pinocamphone has been converted to α-pinene (page 116). It may exist in two isomeric forms, epimers at the carbon atom adjacent to the carbonyl group, and with acid or base an equilibrium mixture is obtained. Corresponding to the two ketones there are four pinocampheols, and their stereochemistry has been elucidated.


OH
(LXXXVIII)
CH2OH
(LXXXVI)
CHO
(LXXXVII)
OH
(LXXXIX)
O
(XC)
COOH
COOH
(LXIX)
DIECKMANN
COOH
COOH
COOH
O
GLYCIDIC
ESTER
COOH
CHO
COOH
O
COOH
COOEt
O
(XCI)
O
(XCII)
O
COOH
OH
COOH
(XCIII)
COOH
H⊕
NCO
O
(XC)

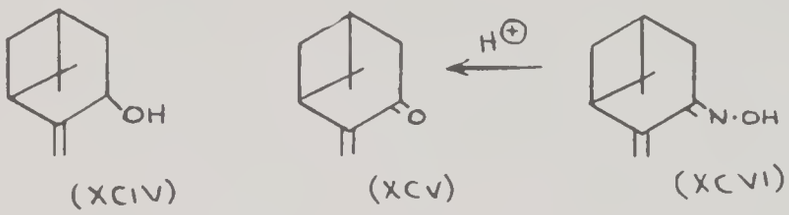
(–)-Pinocarveol (XCIV) occurs in *Eucalyptus globulus*. The corresponding ketone, (–)-pinocarvone (XCV), is found in the same source. Pinocarvone is also obtained from α-pinene nitrosochloride by elimination of hydrogen chloride to give nitrosopinene (XCVI) and hydrolysis with oxalic acid. (+)-Pinocarvone is obtained from β-pinene by selenium dioxide oxidation. The epimer of pinocarveol has been prepared by Ponndorf-Meerwein reduction of pinocarvone.

Myrtenol (LXXXVI) was first obtained from the leaves of *Myrtus communis* L., but was later found elsewhere, e.g., in *Eucalyptus globulus*. Its constitution was shown by conversion to α-pinene and by oxidation to the aldehyde, the latter being also found in false camphor wood. Both compounds, under varying conditions, are obtained by selenium dioxide oxidation of α-pinene.

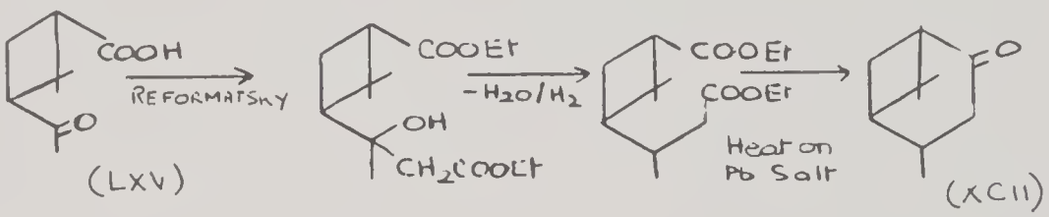
Verbenol (LXXXII) occurs in the oil from the oleoresin of *Boswellia carterii*, and is obtained by autoxidation of α-pinene. Oxidation gives the ketone verbenone, also isolated from *Verbena triphylla*. Catalytic hydrogenation of verbenone affords the saturated ketone verbanone (XCII). This has also been obtained from pinononic acid (LXV) (22) (page 116), by the steps shown opposite.

THE SANTENE GROUP

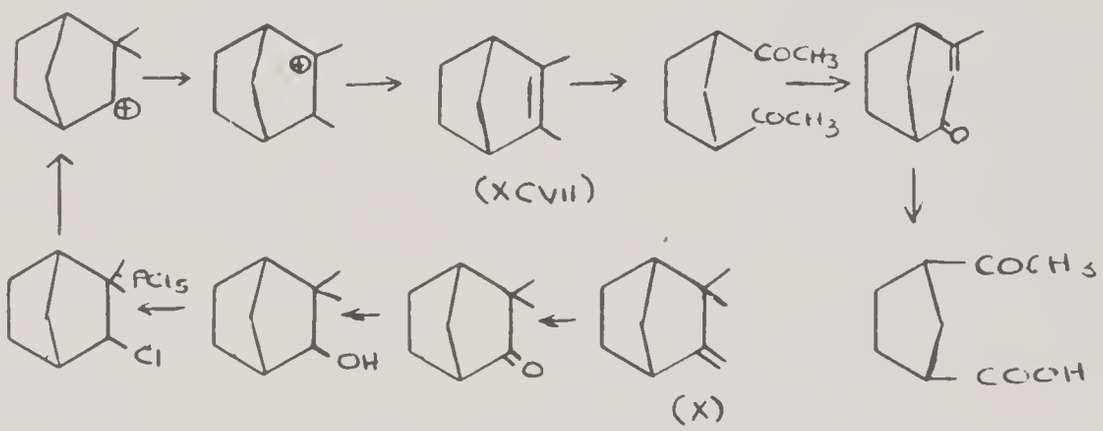
This small group of compounds is structurally related to the camphane and *iso*camphane compounds. **Santene** (XCVII) occurs in East Indian sandalwood oil, and in various pine needle oils. Its structure has been proven, as shown opposite (23), and it has also been obtained from camphene (X) by oxidative removal of the methylene carbon atom, reduction, and a Nametkin change. The elimination of the proton can proceed only in one direction since elimination towards the bridgehead to give a structure of the type (XCVIII) would be a contravention of Bredt's rule. This rule states that in small bridged systems (2:2:1, 2:2:2) a double bond at a bridgehead would introduce too much strain for the molecule to be stable. Put another way, in such molecule *p*-orbitals on the relevant carbon atom are placed so that they cannot overlap (24). The requirements for double bonds at a bridgehead in a transition state, on the other hand, are apparently less stringent, particularly in molecular reactions, e.g., in the conversion of (XCIX) into (C) (25).



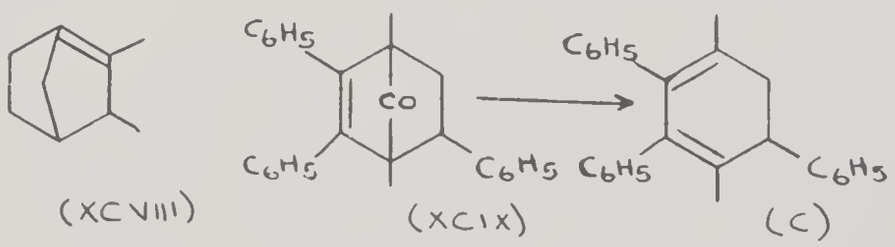
(XCIV) (XCV) (XCVI)



(LXV) (XCII)



(XCVII) (X)

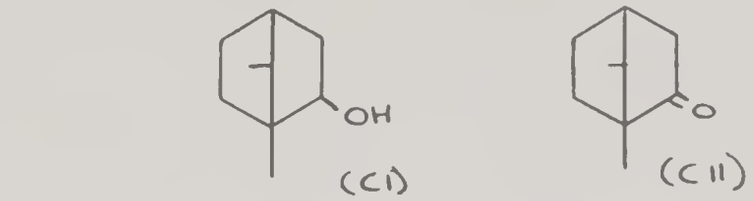


(XCVIII) (XCIX) (C)

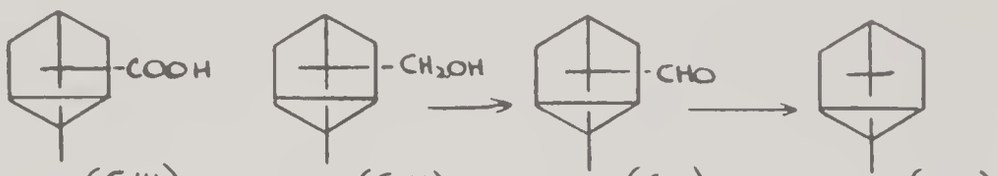
Related alcohols [as (CI)] and the ketone santenone (CII), both having a rearranged carbon skeleton, have also been isolated from the same source. Santenone can also be prepared by oxidation of santene with chromic–sulphuric acid; this process involves a Wagner–Meerwein change. Some interesting tricyclic derivatives are also isolated from sandalwood. These include teresantalic acid (CIII) and the related primary alcohol, teresantalol (CIV). The latter, by oxidation with chromic acid, was converted to the aldehyde (CV), Wolff-Kishner reduction of which gave tricyclene (CVI) (page 140). Teresantalic acid methyl ester on treatment with formic acid gives the lactone (CVII) which could be interpreted as a non-Markownikoff opening of the *cyclo*propane ring to give the ion (CVIII). The results are better interpreted on the assumption of Markownikoff opening to the ion (CIX) followed by a 1:2 shift to the ion (CVIII). This then attacks the ester or carboxyl group to form the lactone. That this is certainly the case is demonstrated by the fact that a similar transformation (26) on the homologous acid (CX) gives the expected γ-lactone (CXI) derived from the ion (CIX). In the *bis*homologated acid (CXII) (27) the ion (CXIII) first formed undergoes a 1:2 shift (Nametkin) to the ion (CXIV) which then gives the γ-lactone (CXV). Thus in systems of such complexity the nature of the original opening of the *cyclo*propane ring may be concealed by subsequent rearrangements.

THE CAMPHANE–ISOCAMPHANE GROUP

Camphane itself and *iso*camphane do not occur in nature. (−)-**Camphene** (X), on the other hand, was first isolated in 1888 (28) and the (+) and (±) forms have since been shown to be fairly widely distributed in nature. Camphene, a crystalline solid, was known for some time before its discovery in nature as being the hydrocarbon derived from "artificial camphor," the product of treating α-pinene (or crude turpentine oil) with hydrogen chloride. It was first obtained pure by Berthelot in 1858 by heating the hydrochlo-

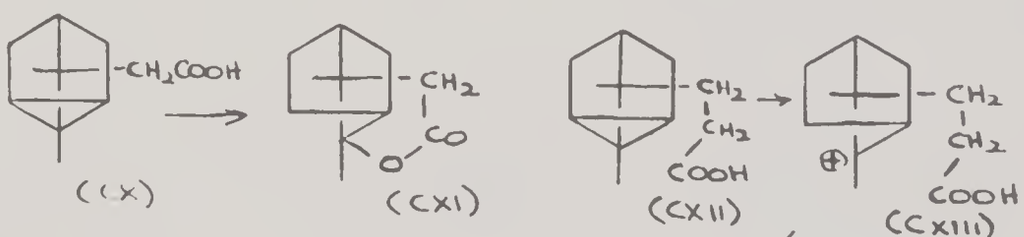


(CI) (CII)

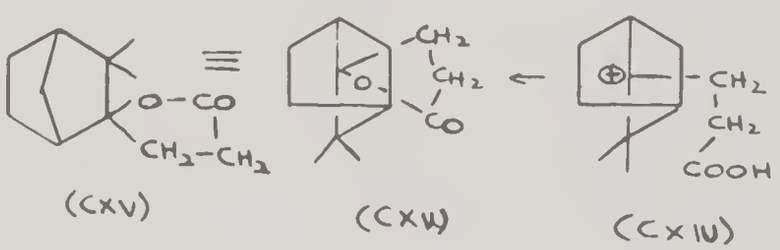


(CIII) (CIV) (CV) (CVI)

(CVII) (CVIII) (CIX)



(CX) (CXI) (CXII) (CXIII)

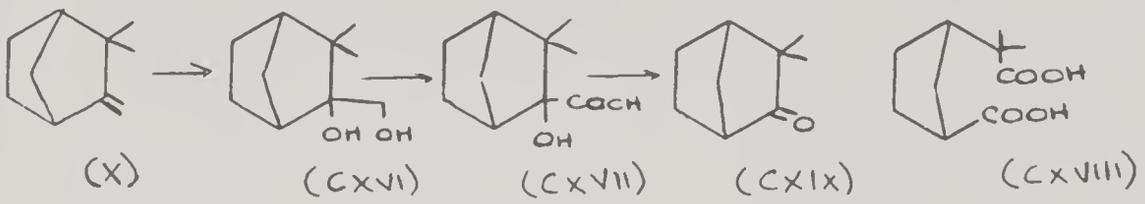


(CXV) (CXIV) (CXIV)

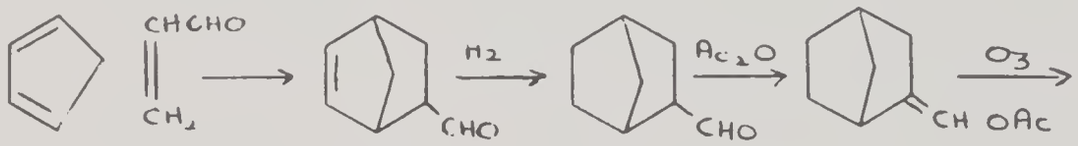
ride with sodium benzoate or sodium stearate. This worker also found that on oxidation it gave camphor.

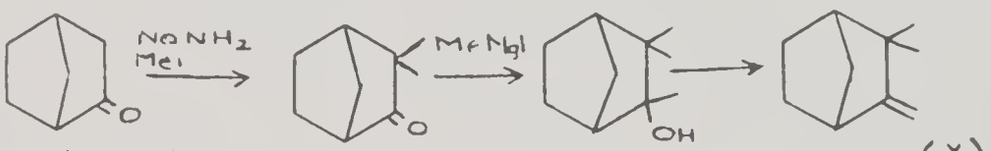
The first important advances came from Wagner (29) who showed that with potassium permanganate it gave a saturated glycol (CXVI); this demonstrated the presence of one double bond and, therefore, of two rings in (X). The acidic products from the oxidation were camphenylic acid (CXVII) and a dicarboxylic acid, camphenic acid (CXVIII). The former acid was shown to be an α-hydroxy acid by its oxidation with lead dioxide to camphenilone (CXIX). This was strong support for Wagner's proposed camphene formula. This was completely established by the synthesis of camphenilone by Komppa and Hintikka (30) in 1914. The synthesis given opposite, however, is that of Diels and Alder.

Camphenilone has also been converted into camphene. Two objections were raised against the Wagner formula. Firstly, the ozonolysis of camphene gave, as well as the expected camphenilone, about an equal amount of dimethylnorcampholide (CXX), the structure of which was known from its synthesis. This was later explained as being a secondary product resulting from degradation of the preformed ketone. However, since the ozonolysis was carried out in acetic acid, the formation of peracetic acid is probable and the transformation of (CXIX) to (CXX) is therefore a normal Baeyer-Villiger reaction. Secondly, since the structure of camphenic acid (CXVIII) was firmly established by synthesis, it has been proposed that its presence is due to its formation from (CXVII) through the α-diketone carbocamphenilone (CXXI). This compound is also said to be formed by the distillation of the lead salt of (CXVII). However, a reversal of a benzilic acid change under such mild conditions is improbable, and the probable precursor of camphenic acid during the oxidation is the hydroxy aldehyde (CXXII), presumably an intermediate in the formation of (CXVII). The action of alkali on this, as shown, leads to (CXXI) in an unexceptional manner (31). Under much more vigorous conditions—fusion with alkali—the hydroxy acid is said to be converted to camphenic acid.

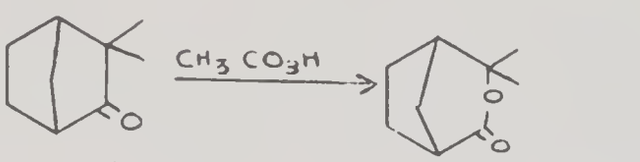


(X) (CXVI) (CXVII) (CXIX) (CXVIII)

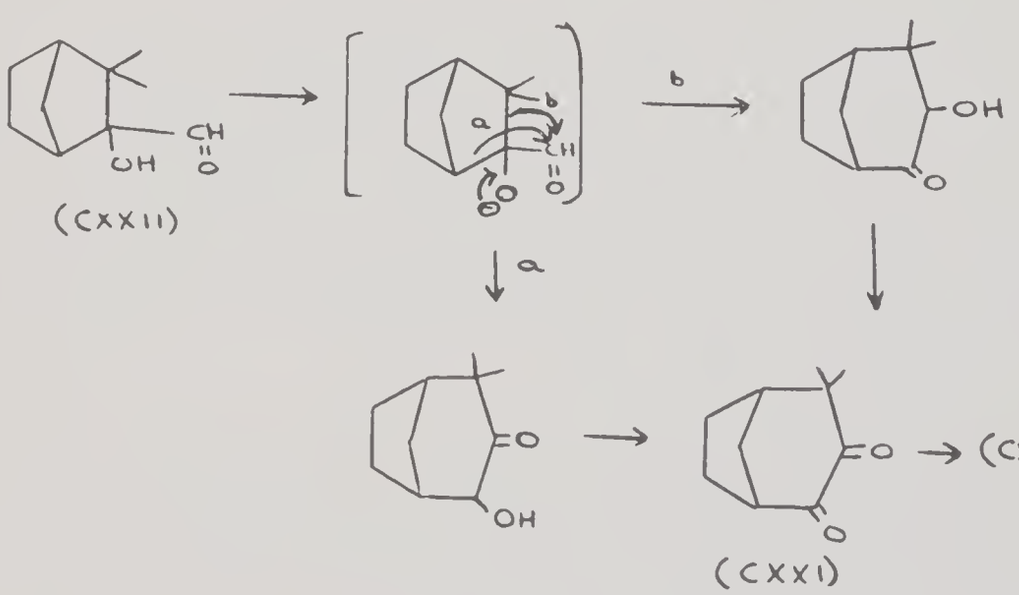




(CXIX) (X)



(CXIX) (CXX)



(CXXII) (CXXI)

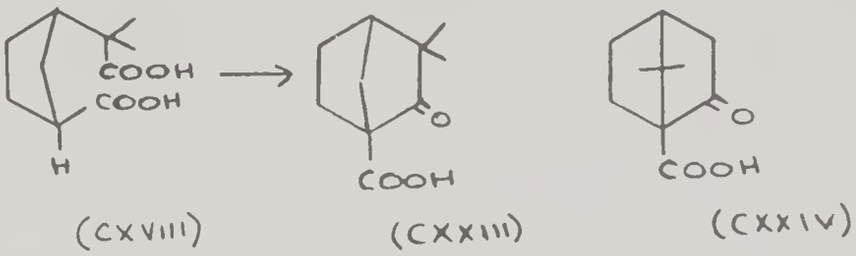
On heating with acetic anhydride camphenic acid (CXVIII) is converted to camphenonic acid (CXXIII). This is a β-keto acid, yet does not decarboxylate since the product (the enol of the ketone) would have a double bond at a bridgehead. With strong alkali (CXXIII) is reconverted to camphenic acid (CXVIII) by nucleophilic attack on the carbonyl group. A similar product, ketopinic acid (its formation involving a Wagner-Meerwein change) (CXXIV), is amongst the products of nitric acid oxidation of camphene.

With hydrogen chloride camphene gives an unstable camphene hydrochloride (CXXV) which rearranges to *iso*bornyl chloride (CXXVI). The rearrangement is strongly catalysed by hydrogen chloride, and by such reagents as cresol, phenol, and stannic chloride. With a mixture of sulphuric acid and acetic acid *iso*borneol acetate is obtained, while with dilute sulphuric acid the product is the alcohol. In alcoholic solution attack by the solvent gives the ethers as the product. Although *iso*borneol derivatives are the *main* products, some of the epimeric borneol derivatives are also formed. An interesting reaction of the norketone camphenilone (CXIX), derived from camphene (page 130), is its transformation under the influence of strong sulphuric acid into *p*-methylacetophenone. The mechanism shown opposite has been proposed by Noyce (49).

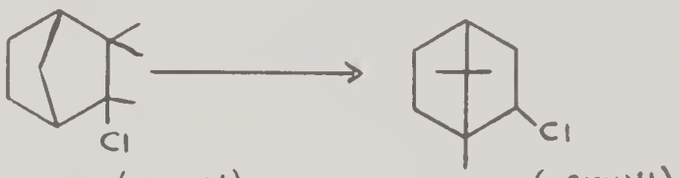
Camphor

This important substance is not very widely distributed in nature and the main source is *Cinnamomum camphora* Nees, which is found in the East in the area from Cochin China to Shanghai, the most extensive forests being in Formosa. It has also been cultivated with success in other parts of the world. Camphor is present in all sections of the tree, but the highest proportion is in the trunk. The camphor from this source is dextrorotatory; the laevorotatory form is less common, sources being the oils from *Blumea balsamifera*, *Artemesia tridentata*, etc.

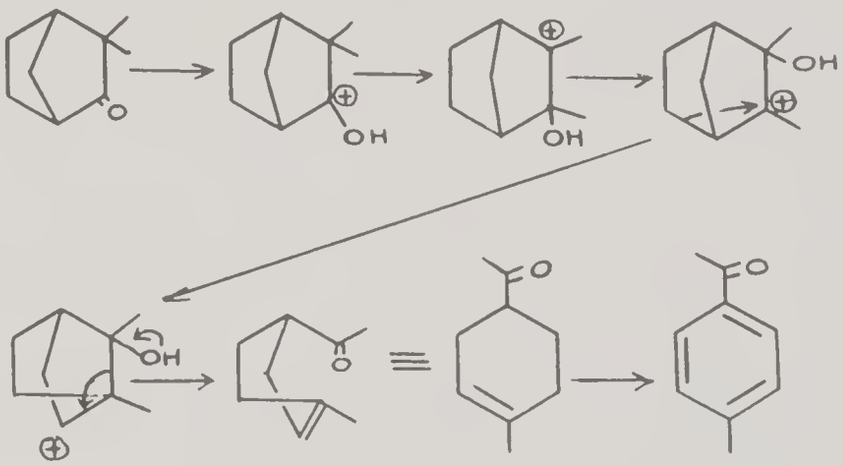
Because of its ease of isolation camphor has been known for many centuries, particularly in China. It was not, on the other hand, known to the Greeks or Romans, but was introduced to Europe by the Arabs to whom it was known under the name of *kamphur* or



(CXVIII) (CXXIII) (CXXIV)



(CXXV) (CXXVI)



kaphur. It was first mentioned by Avicenna, and Serapion called it cáfúr. A more detailed description was given by Symeon Seth in the eleventh century.

Formerly, Venice held the monopoly of refining camphor, but production later passed to England, France, Holland, and Germany. The bulk is now manufactured, by various processes, from α-pinene obtained from oil of turpentine, but it is interesting that even in 1864 the import of camphor into England was registered as about 1000 tons, over 90% of which was, however, re-exported. The purification was effected by taking advantage of the great volatility of camphor. A simple method of historic interest is described in the Chinese Materia Medica 34.17 (32). The felled tree is chopped and the fragments soaked in boiling water. After some days the mixture is filtered and the camphor crystallised. Camphor also was purified by spreading crude camphor and earth in alternate layers in a pan, covering, sealing, and heating carefully so that the camphor sublimed into the upper pan.

Camphor is used as a plasticiser for the production of celluloid and photographic film, for smokeless powders and explosives, and for medicinal purposes. It has a large molecular freezing point depression constant of which use has been made in the well-known Rast method for the determination of molecular weights. It is also an insect repellent. The younger scientist, in the nursery, often manifests an interest in camphor, for when fragments are thrown on water the surface tension changes cause them to shoot rapidly about the surface.

A very considerable amount of effort was employed in the elucidation of the structure of camphor. Investigations date from Libavius (1595) through Robert Boyle (1667) to Lavoisier and later to Dumas (1833). Even after 1870, well over a dozen formulae were proposed and considered. The result of this enormous bulk of work led

finally to the formulation (CXXVII) proposed by Bredt in 1893 (33). His researches, apart from their intrinsic interest, are of much historical importance. From them the following requirements for a satisfactory structure emerged:

1. It had the formula $C_{10}H_{16}O$.

2. Since it formed an oxime and a semicarbazone, it contained a carbonyl group. In confirmation it was reduced to the corresponding alcohol, borneol, from which it could be recovered by oxidation. Oxidation did *not* give a monocarboxylic acid containing the same number of carbon atoms; it was therefore a ketone.

3. There was a methylene group adjacent to the carbonyl group because it formed, with nitrous esters, an *iso*nitroso compound and with formates an hydroxymethylene compound. Further, vigorous oxidation gave a dicarboxylic acid, camphoric acid (CXXVIII), without the loss of carbon.

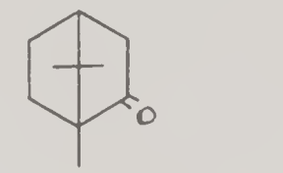
4. Molecular refraction and other studies on camphor and on camphoric acid showed they contained no carbon-carbon unsaturated linkage; camphor must therefore, on the basis of the empirical formula, be bicyclic (34).

5. On bromination camphoric anhydride gave a monobromo compound showing the presence of one hydrogen atom α to a carbonyl group. Since two different series of half esters were also obtainable, the part formula (CXXIX) was therefore established.

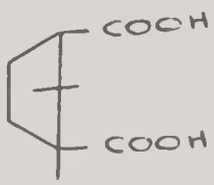
6. By oxidation with nitric acid a tribasic acid was obtained together with camphoric acid. This substance, camphoronic acid, was shown to be $\alpha:\alpha:\beta$-trimethylcarballylic acid (CXXX) by the synthesis summarised opposite (35). This acid is important because it contains nine of the original ten carbon atoms.

7. Treatment of camphor with sodium followed by cyanogen, and subsequent hydrolysis, gives with cleavage of the β-ketonitrile, homocamphoric acid (CXXXI). Bromination of this and dehydrobromination gives dehydrohomocamphoric acid (CXXXII) proving that the carbon atom at the bridgehead adjacent to the original methylene group bore a hydrogen atom.

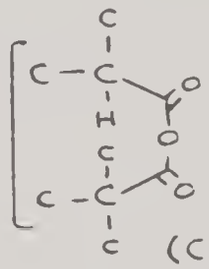
Also, camphoric acid on heating with acetic anhydride gave the anhydride of a glutaric acid, as would be expected from the Blanc



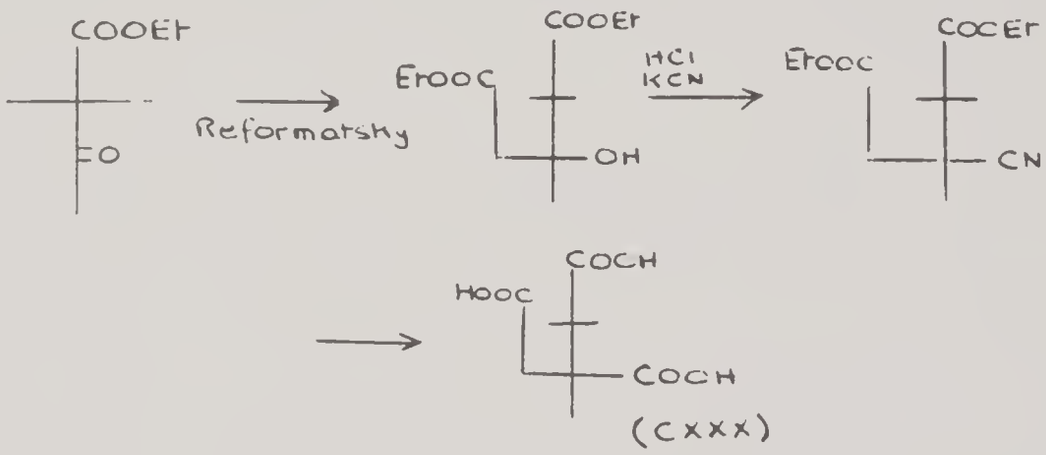
(CXXVII)



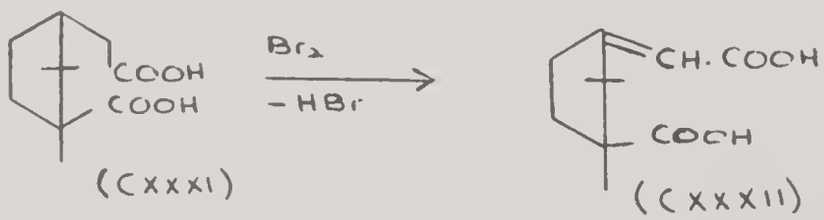
(CXXVIII)



(CXXIX)



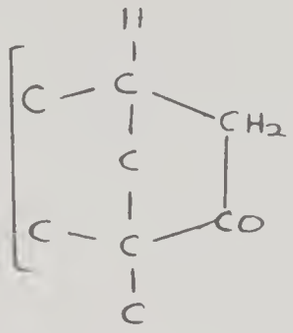
(CXXX)



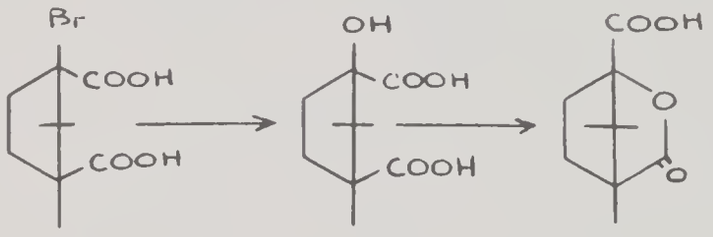
(CXXXI) (CXXXII)

rule. According to this rule (36) higher dicarboxylic acids give ketones. For example, adipic acid under the same treatment gives *cyclo*pentanone. Homocamphoric acid gave accordingly the ketone which is, in fact, camphor. This evidence for the partial structure (CXXXIIa) was supported by the hydrolysis of bromocamphoric acid (CXXXIII) to hydroxycamphoric acid (CXXXIV). This compound remains as the hydroxydicarboxylic acid only as it salts. On acidification it lactonises; this behaviour is suggestive of a γ-lactone though it is not compelling.

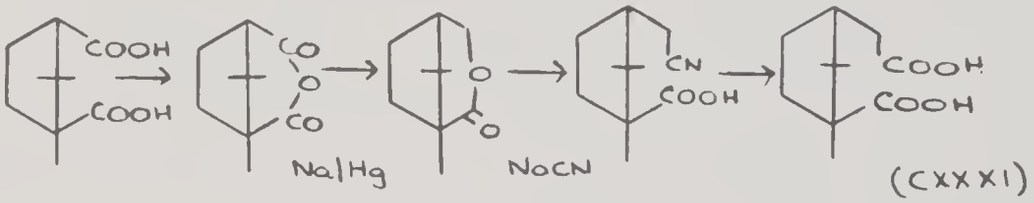
This work culminated in the almost simultaneous synthesis by Komppa, and by Perkin and Thorpe, of camphoric acid (37). Since this had been converted into homocamphoric acid (CXXXI) some years previously by the steps shown, and the latter gave camphor on distillation of the calcium salt, these two syntheses of camphoric acid constituted total syntheses of camphor. Of the two, that shown opposite, Komppa's, is the better since both the steps involved and the starting material are simpler; the camphoric acid was resolved.



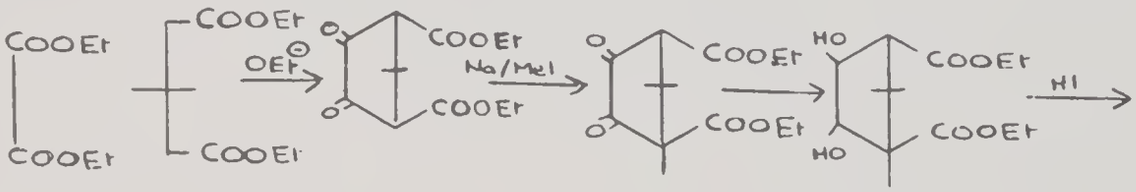
(CXXXIIa)

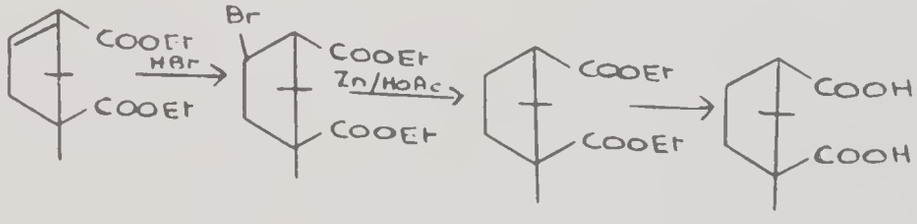


(CXXXIII) (CXXXIV)



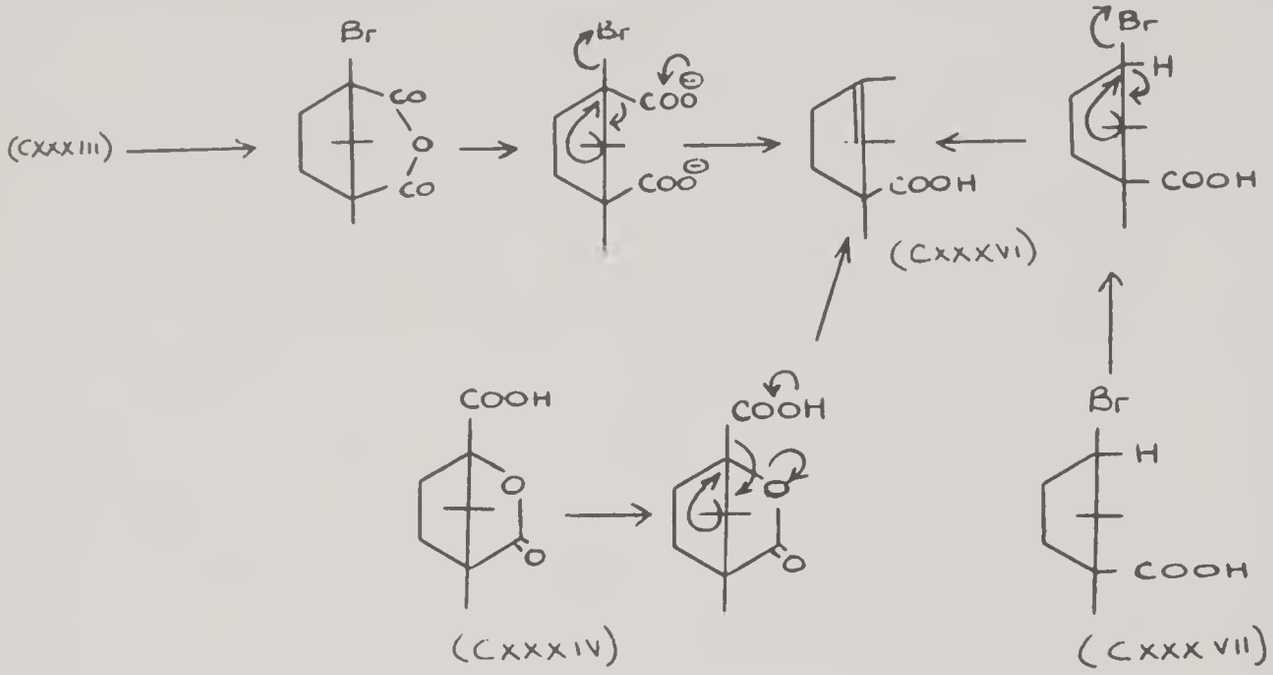
(CXXXI)

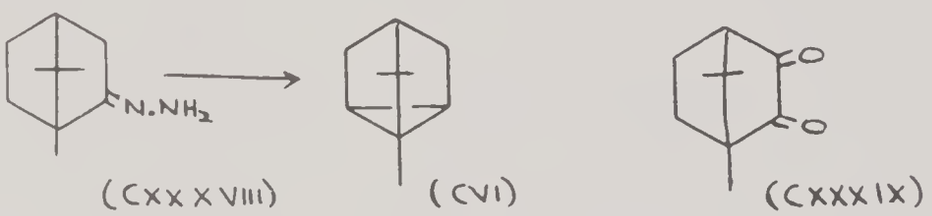


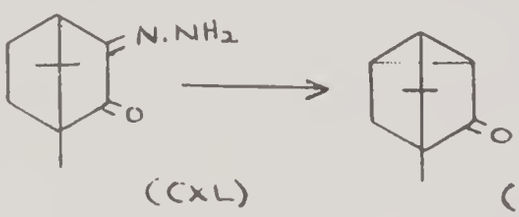


α-Bromocamphoric acid (CXXXIII) may be converted into the anhydride, which on heating with water or, better, sodium carbonate solution, undergoes an interesting transformation to give as well as camphoric acid some laurolenic acid (CXXXVI) (38). The driving force may be the solvolysis of the *neo*pentyl-type bromide followed by Nametkin rearrangement and decarboxylation. Support for the first stage is found in the fact that with base bromocamphonanic acid (CXXXVII) rearranges to (CXXXVI) (39), whilst support for the second stage is suggested by the fact that (CXXXVI) is obtained by the distillation of camphanic acid (CXXXIV). A close analogy for the conversion of (CXXXIII) to (CXXXVI) is found in the chemistry of cedrene (page 284).

Camphor, as already mentioned, forms carbonyl derivatives in the normal fashion. The hydrazone (CXXXVIII) when treated with (40) yellow mercuric oxide in alkaline solution is oxidised with the evolution of nitrogen, to give an electronically deficient carbon atom (carbene). Hydrogen transfer then takes place to give the saturated tricyclic hydrocarbon tricyclene (CVI), also obtained from teresantalic acid. The oxime of camphor on dehydration gives α-campholenonitrile (page 119). The *iso*nitroso derivative of camphor (camphorquinone monoxime) on hydrolysis gives camphorquinone (CXXXIX) which is, however, better prepared by the action of selenium dioxide on camphor. The monohydrazone (CXL), when oxidised with mercuric oxide, also forms a *cyclo*propane to give β-peri*cyclo*camphenone (CXLI). Two other reactions of camphorquinone are of interest. With diazomethane ring expansion takes place to give a β-diketone which enolises, then forming the methyl

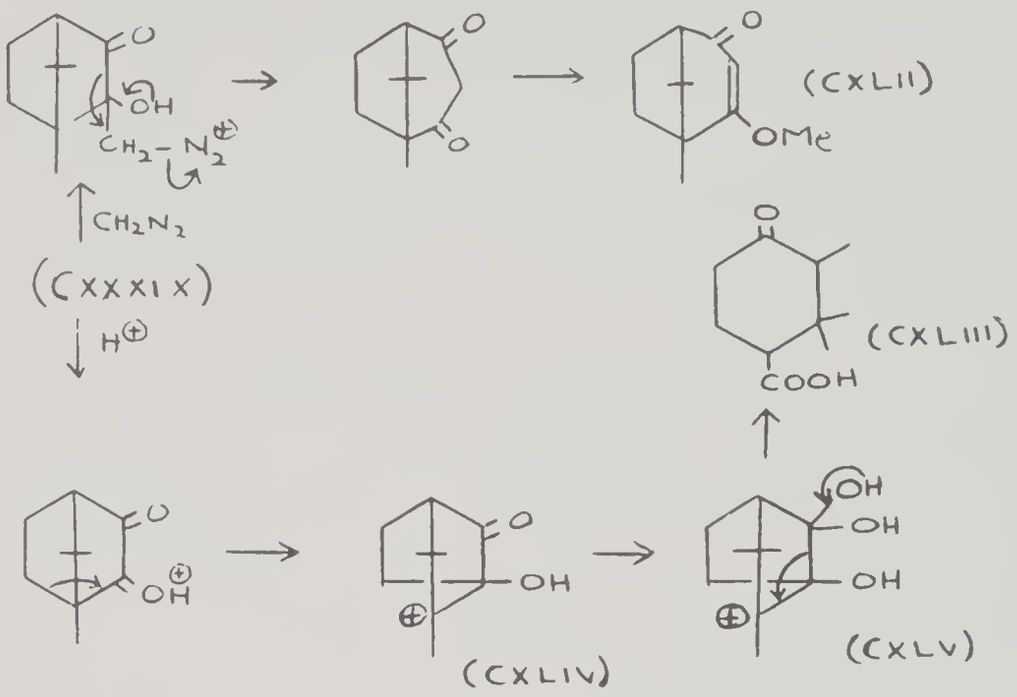

(CXXXIII)
Br
CO
O
CO
Br
COO⊖
COO⊖
COOH
(CXXXVI)
Br
H
COOH
COOH
COOH
(CXXXIV)
Br
H
COOH
(CXXXVII)

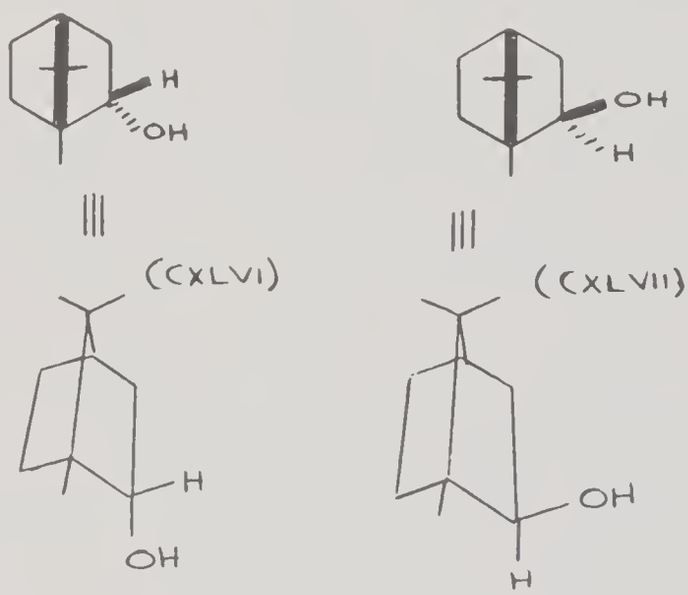

N.NH2
(CXXXVIII)
(CVI)
O
O
(CXXXIX)

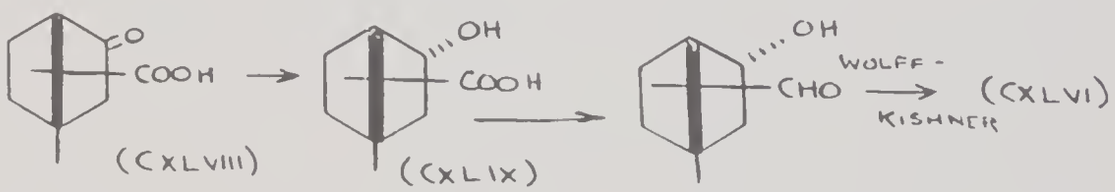

N.NH2
O
(CXL)
O
(CXLI)

ether of the acidic hydroxyl (CXLII). With concentrated sulphuric acid a complex rearrangement takes place to give the (41) monocyclic keto acid (CXLIII). A possible mechanism is through the ions (CXLIV) and (CXLV). The structure of the product has been confirmed by synthesis.

Borneol and ***iso*borneol** are the stereoisomeric alcohols related to camphor and have the configurations shown in (CXLVI) and (CXLVII), respectively. Borneol is fairly widely distributed both in the free state and as esters. (+)-Borneol or "Borneocamphor" is found in *Dryobalanops aromatica* Gaertn., (–)-borneol or "Ngai-camphor" in *Blumea balsamifera*, and the racemate in other oils. Both alcohols are formed in varying proportions in several reactions. These include the reduction of camphor with sodium and alcohol and the hydration of pinene and camphene. Reduction of *iso*ketopinic acid (CXLVIII) with sodium and alcohol gave (CXLIX) mainly in the *endo* form (hydroxyl on the opposite side of the plane of the ring from the bridge. This was separable from its isomer (which was present as a lactone) and by the stages shown (CXLIX) was then converted to borneol. This must also, therefore, have the *endo* configuration. This evidence, as such, is persuasive but not compelling. This is because, under the vigorous alkaline condition (sodium ethoxide) used in the Wolff-Kishner reduction, epimerisation of alcohols to the more stable configuration, by an oxidation-reduction process (51), is known to take place. An example is the


(CXXXIX)
(CXLII)
(CXLIII)
(CXLIV)
(CXLV)

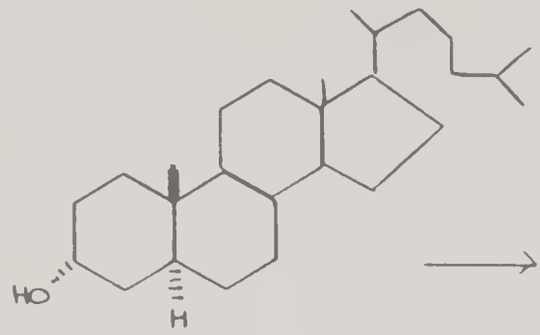

(CXLVI)
(CXLVII)


(CXLVIII)
(CXLIX)
WOLFF - KISHNER
(CXLVI)

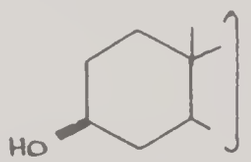
conversion of *epi*cholestanol (axial) (CL) to cholestanol (equatorial) (CLI) (42). However, in the present case, control experiments showed that *iso*borneol was not isomerised to borneol under the conditions used. The allocation of configuration has been amply confirmed by other chemical and physical evidence. Racemic borneol has been synthesised by an application of the Diels-Alder synthesis (43).

Bornyl chloride was one of the first camphene derivatives known, being, as already mentioned, prepared by the action of hydrogen chloride on pinene (artificial camphor). Its structure was confirmed by vigorous oxidation to ketopinic acid (CXXIV) and camphoric acid and by reduction to the saturated hydrocarbon, camphane, with sodium. It was also prepared, in small yield, from borneol by the action of phosphorus pentachloride, the main product being, however, *iso*bornyl chloride. The elimination of hydrogen chloride leads to camphene. This and the related alcohol *iso*borneol are important for camphor production (by oxidation) and their preparation has been extensively studied.

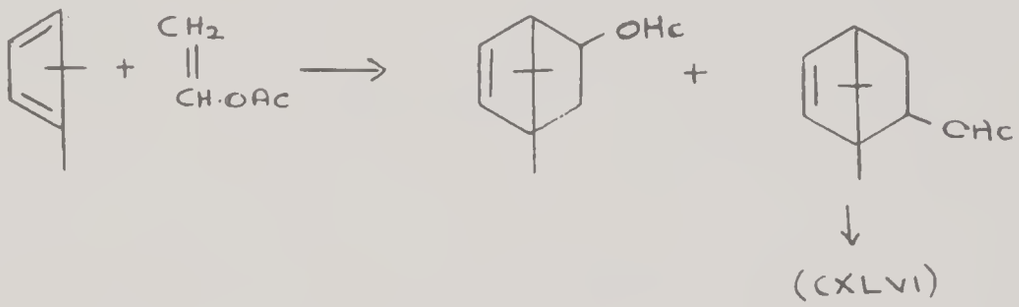
Although the elimination of hydrogen halide from bornyl and *iso*bornyl chlorides leads essentially to camphene, conditions may be chosen which lead, at least in part, to the unrearranged hydrocarbon bornylene (CLII): it may be obtained, for instance, by the action of very strong alkali on bornyl iodide. It has also been prepared by pyrolysis of the xanthate, but in this case some tricyclene is formed at the same time. Pure bornylene has been obtained by the Hofmann degradation of (CLIII), or by the more complex series of steps shown opposite from camphor (44). The unsaturated acid (CLIV) could not itself be decarboxylated. $\alpha:\beta$-Unsaturated acids which do decarboxylate are believed to isomerise under the conditions of the experiment to $\beta:\gamma$-unsaturated acids which then decompose by a cyclic mechanism (45) during which the double bond moves back into its original position as shown opposite.



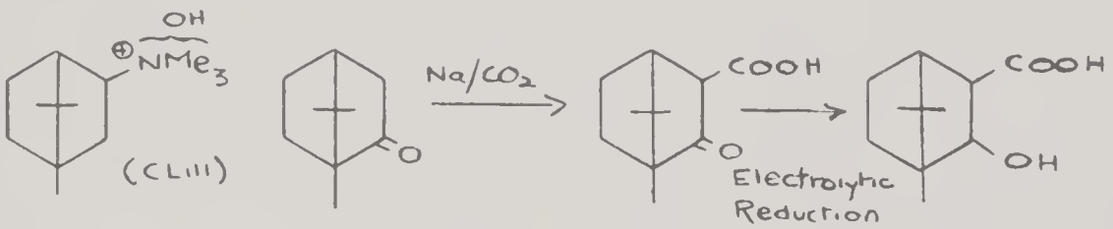
(CL)



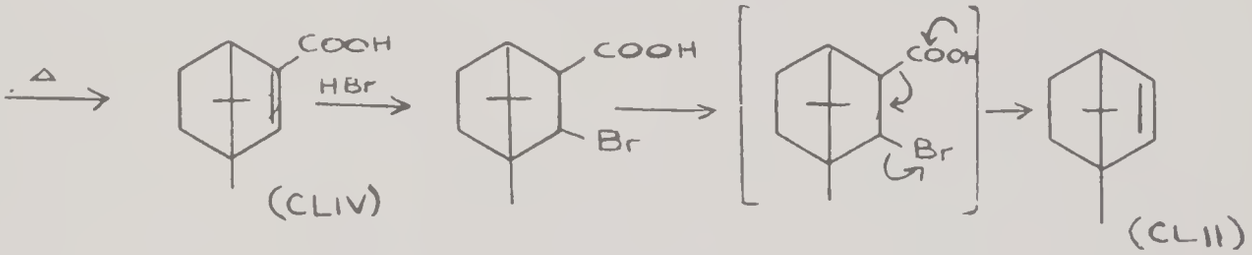
(CLI)



(CXLVI)

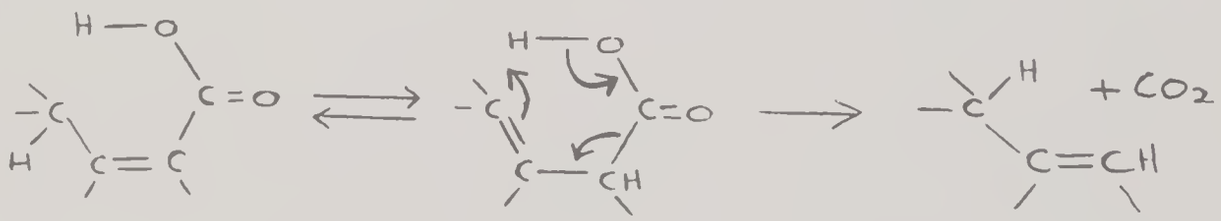


(CLIII)



(CLIV)

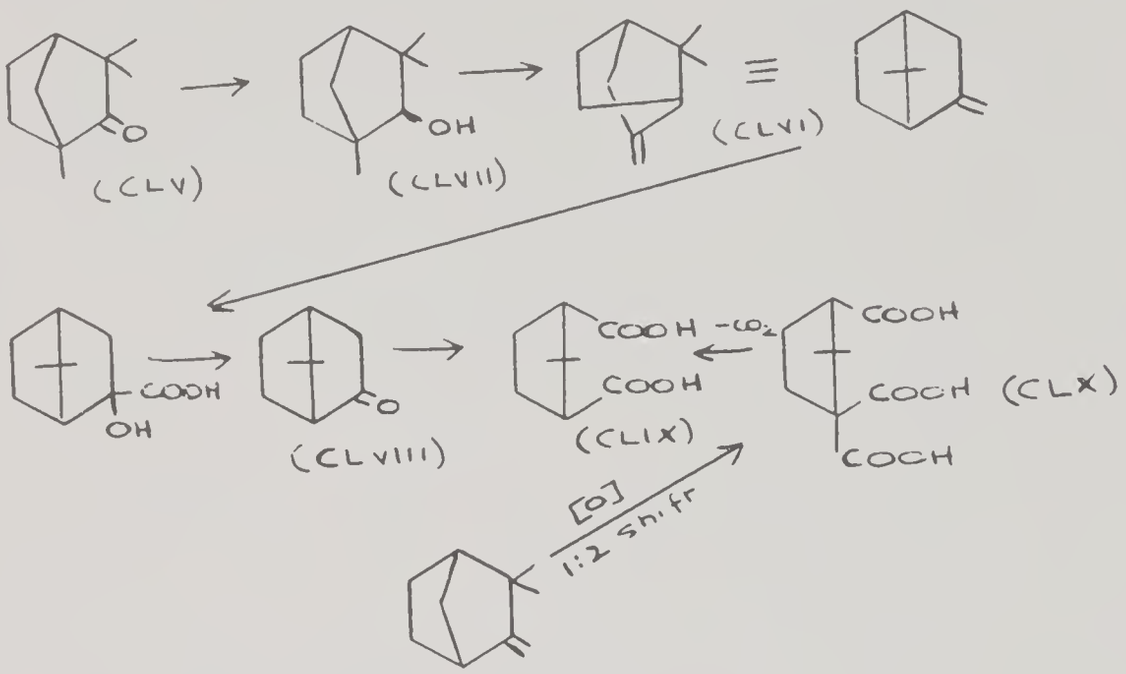
(CLII)

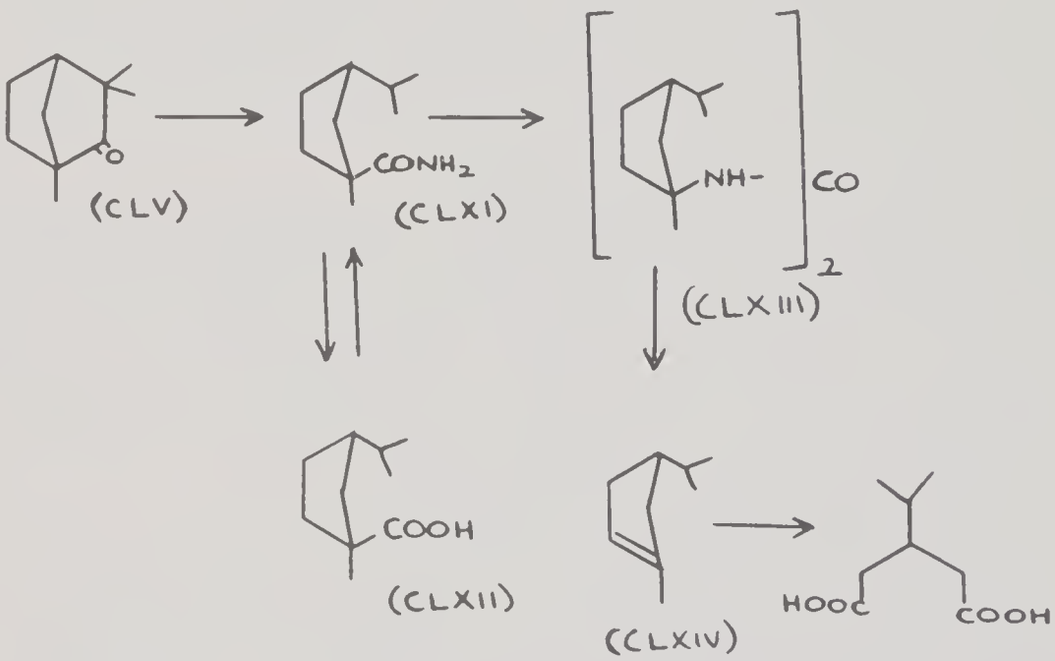


The Fenchane–Isobornylane Group

The most important member of this group of substances is the ketone, **fenchone** (CLV), which occurs in the oil of fennel and in thuja oil. It presented to the early workers a more difficult structural problem than did camphor because there was no methylene group adjacent to the carbonyl function to assist degradation. The first successful degradation attempts were based on α-fenchene (CLVI), a hydrocarbon obtained by the dehydration of α-fenchyl alcohol (CLVII). The latter, in turn, was obtained by the reduction of fenchone. α-Fenchene was oxidised to an α-hydroxy acid by potassium permanganate, this on being cleaved by lead dioxide gave α-fenchocamphorone (CLVIII). Nitric acid oxidation of this gave apocamphoric acid (CLIX), also obtained (through carboxyapocamphoric acid (CLX)) by the action of nitric acid on camphene. The structure of (CLIX) had been confirmed by synthesis (46). This degradation establishes the formula of α-fenchene, but since α-fenchene is not the only hydrocarbon produced in the dehydration of α-fenchyl alcohol this does not provide evidence for the structure of fenchone, which indeed showed no indication of the presence of a hydrogen atom in the α position. The correct structure was obtained from the cleavage product of fenchone with sodamide, fencholamide (CLXI), which could be hydrolysed to the acid, fencholic acid (CLXII). This amide, with bromine in alkali, gave the urea (CLXIII) which with sulphuric gave a hydrocarbon, apofenchane, the structure (CLXIII) of which was shown by oxidative degradation (47).

The structure of fenchone was finally confirmed by synthesis (48) and by preparation from camphenonic acid (CXXIII) by conversion of the carboxyl to methyl by standard methods. The conversion of α-fenchyl alcohol to α-fenchene, therefore, involves a 1 : 2 shift. Fenchone hydrazone on oxidation with mercuric oxide decomposes in the same way as camphorhydrazone, yielding in this case *cyclo*fenchene (CLXV), whilst the oxime with acid is cleaved to a mixture of nitriles both involving scission of a carbon–carbon bond $\beta : \gamma$ to the oxime, as in the case of campholenic acid (page 119).


O
(CLV)
OH
(CLVII)
≡
(CLVI)
COOH
OH
(CLVIII)
O
COOH
COOH
(CLIX)
-CO₂
COOH
COOH
COOH
(CLX)
[O]
1:2 shift


O
(CLV)
CONH₂
(CLXI)
NH-
CO
2
(CLXIII)
COOH
(CLXII)
(CLXIV)
HOOC
COOH

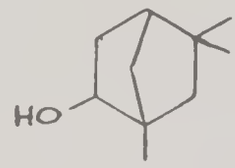
(CLXV)

α-Fenchyl alcohol, apart from being obtained by the reduction of fenchone with sodium and alcohol, also occurs in nature, being found in the oil from the roots of *Pinus palustris*. It is produced in the hydration, with rearrangement of both α- and β-pinene. *iso*-Fenchyl alcohol (CLXVI) does not occur in nature, but may be prepared by the hydration of α-fenchene with sulphuric acid–acetic acid. Oxidation then gives *iso*fenchone (CLXVII). The constitution of *iso*fenchone was shown by oxidation with permanganate to (CLXVIII), the latter having been synthesised; *iso*fenchone has also been synthesised.

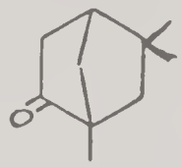
The hydration of α-fenchene to *iso*fenchyl alcohol is a process which it does not appear possible to write exclusively on the basis of 1 : 2 shifts, and *cyclo*fenchene (CLXV) has been postulated as an intermediate, though more recent work (page 168) has established that this is a 1 : 3 hydrogen transfer. *Cyclo*fenchene has been shown to give *iso*fenchyl alcohol with acids. The *direct* cleavage of *cyclo*fenchene to the ion (CLXIX) is extremely improbable, representing as it does *non*-Markownikoff addition of the proton to the *cyclo*propane ring; similar considerations apply to the cleavage of tricyclene (see, however, page 128).

A number of other hydrocarbons are known in this series, not many of which have been obtained pure. β-Fenchene (CLXX) is obtained by the dehydration of α-fenchyl alcohol using potassium hydrogen sulphate and by the dehydrochlorination of *iso*fenchyl chloride (CLXXI). *Iso*bornylane (α-fenchane) may be obtained by the hydrogenation of α-fenchene; the Wolff-Kishner decomposition of fenchone hydrazone gives fenchane.

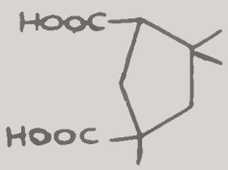
A reaction in this series which is of particular interest is the conversion of fenchylamine (CLXXI) to, amongst other products, limonene by the action of nitrous acid (50). This would seem to require isomerisation to the pinane series prior to cleavage, as represented in simplest terms opposite.



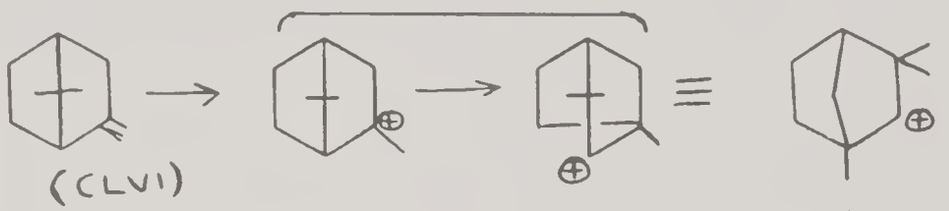
(CLXVI)

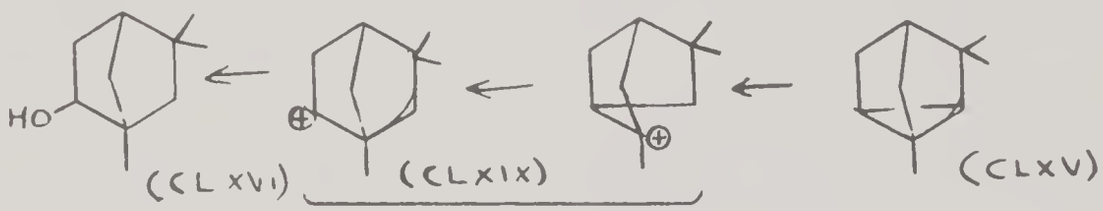


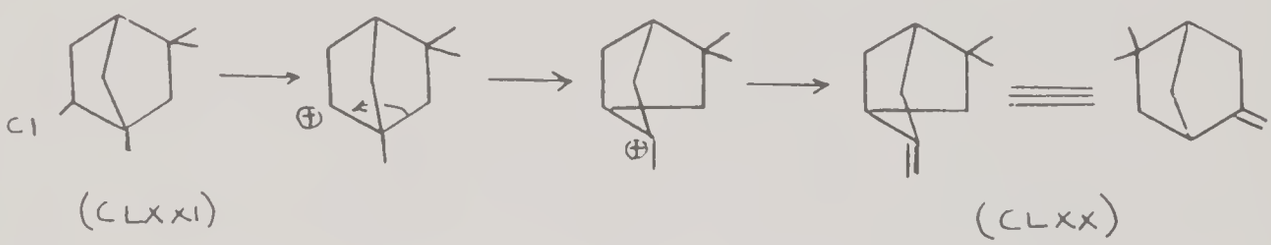
(CLXVII)

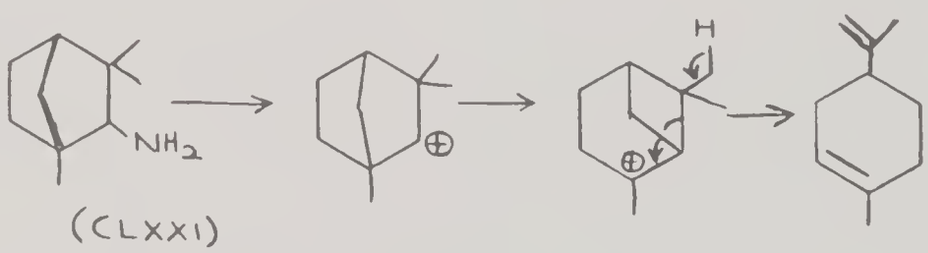


(CLXVIII)









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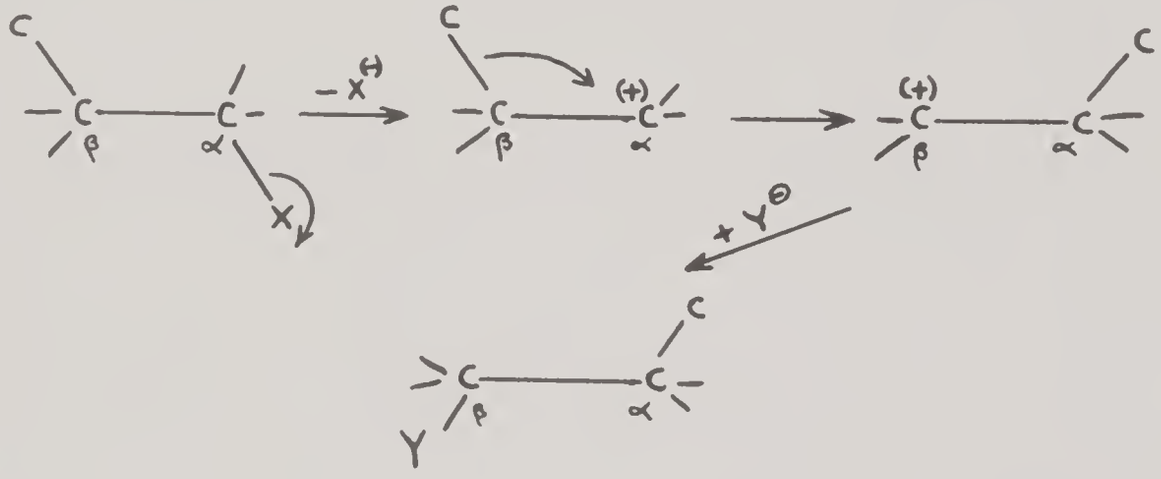
THE BICYCLIC MONOTERPENOIDS: II

In the description of the behaviour of the terpenoids so far covered, the discussion of mechanism and of the related stereochemical and stereoelectronic factors has been kept to a minimum. It has been sufficient to recognise the existence of 1:2 shifts and to classify them as being Wagner-Meerwein or the related Nametkin changes. A closer inspection of what is now a considerable amount of published work led several workers to investigate the more intimate details of these changes and also associated rate phenomena. As a result, the concept of the ion involved in these changes has broadened and, further, by the use of tracers it has been shown that apparently simple changes may in fact be very complex and involve a considerable amount of skeletal reshuffling (43).

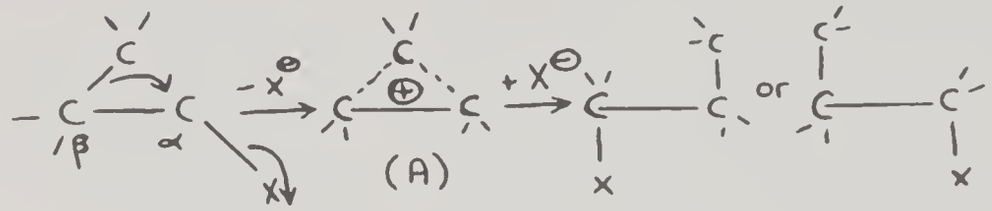
The most general mechanism for the Wagner-Meerwein rearrangement, not now being restricted to terpenoids, would seem to require a preliminary ionisation (1-3). The carbonium ion at C_α then formed can rearrange by the shift of a β-electron pair to give a new carbonium ion at C_β. This may be illustrated as shown opposite. It is evident from both stereochemical and kinetic data that this representation is over-simplified. In particular, it is shown that asymmetry at *both* C_α and C_β is usually retained during the rearrangement. Yet, if the carbonium ions indicated were sufficiently long lived, no such stereospecificity could be expected. Therefore it must be concluded that the entire process—ionisation, rearrangement, and discharge of the new cation—takes place concertedly, or

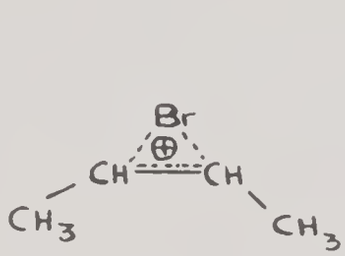

C
C
β
C
α
X
−X⊖
C
C
β
(+)
C
α
(+)
C
β
C
C
α
+Y⊖
C
C
β
C
α
Y

the carbonium ion intermediate(s) exist in the form of some modified, "non-classical" ion in which the stereochemistry is retained.

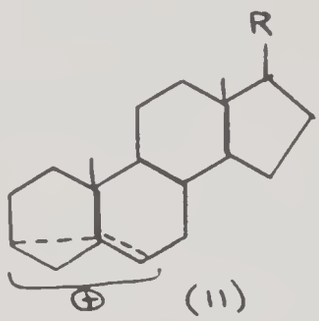
Such a species is the "bridged" cation (A) in which the bridging carbon is somewhere (42) between C_α and C_β, and the positive charge is distributed amongst these centres (4,5,22,37). The direct formation of (A) involves the *participation* of the C_β electron pair in a "backside" attack on C_α, and is thus analogous to Walden inversion. The subsequent solvolysis of (A) at either C_α or C_β involves a similar inversion. The net result would be retention at C_α and inversion at C_β as indicated. The ionisation, it may be noted, may be *assisted* by the participation of the adjacent neighbouring group when leading to the bridged *anchimeric* or *synartetic* ions. Examples of such bridged ions are those, for instance, formed by the participation of bromine in (I) and of the ethylenic linkage in (II) which is an intermediate in the *i*-cholesterol rearrangement (7). The participation of phenyl in the 3-phenyl-2-butyl cation (6) is similar. The effect of the intervention of the ion (I), for instance, in the bromination of but-2-ene is to impose a stereochemical restriction on the course of the addition of the anion. The *threo* product, produced by Walden inversion at either centre, is the result.

The above description, however, is not immediately relevant to the Wagner-Meerwein rearrangement. In case (I) the participation is of a non-bonding electron pair on the halogen, and in (II) and (III) of the mobile π-electrons of unsaturated systems. In general the conditions for participation (8) are the existence of an incomplete shell of electrons and a low ionising potential for the donating electrons. In the rearrangements of present interest the donated electrons constitute a C–C bond. If the stereochemical factors are conducive to participation then the actual intermediate state will, if migration occurs, depend on the initial and final energy states. Since a carbon–hydrogen bond has a potential higher than that of a carbon–carbon bond, it might be expected that, in a situation in which rearrangement is possible, participation (if geometrically feasible) will involve the latter rather than the former. That is, other factors being equal, a methyl group migrates in preference to hydrogen.

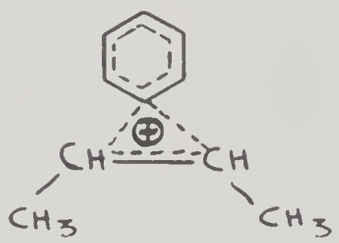




(I)



(II)

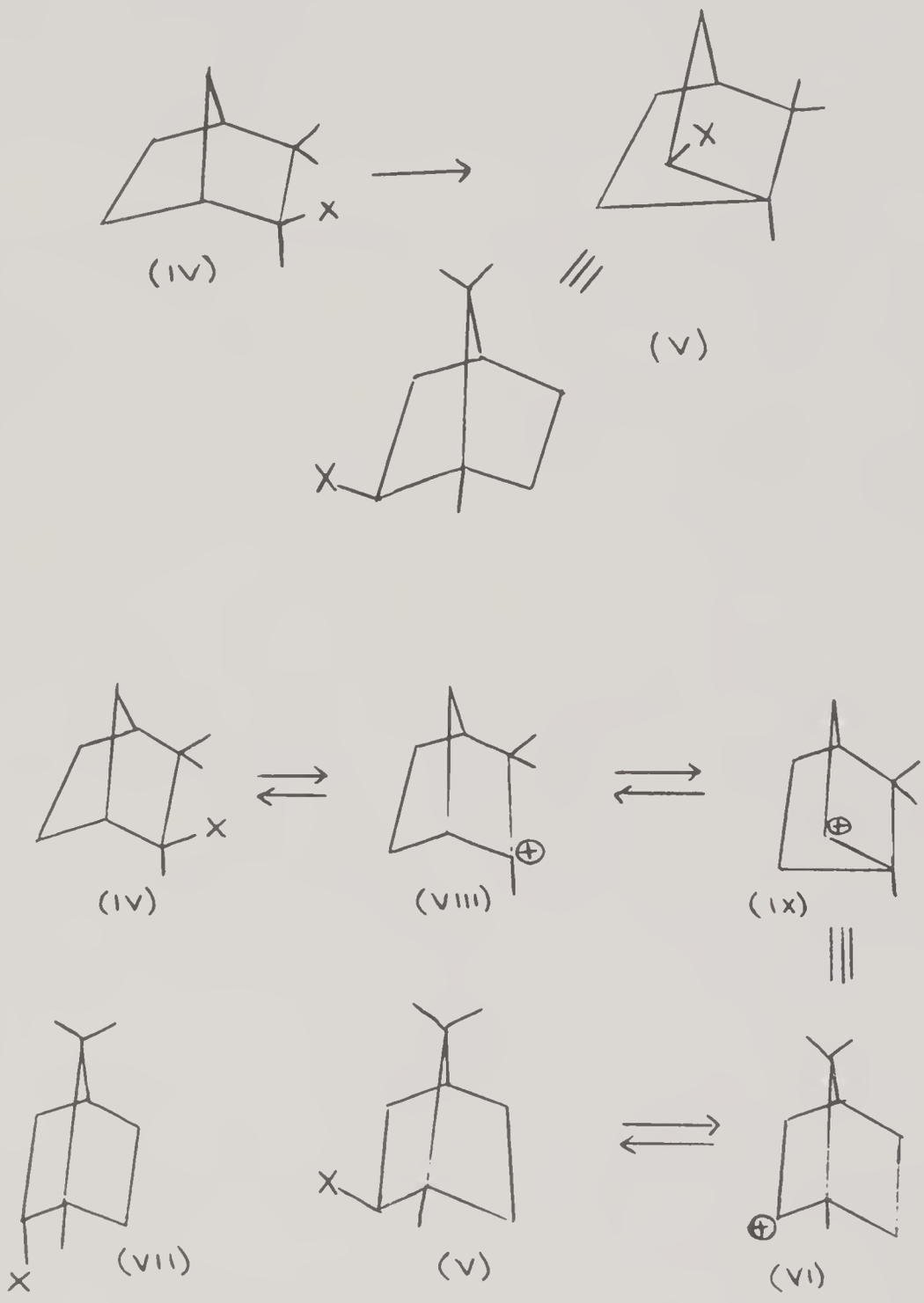


(III)

Assuming stereochemical integrity to be maintained, varying degrees of discontinuity from a completely concerted reaction to a very stable "bridged" ion are possible. Before the recently available evidence for bridged ions in the terpenoid series is reviewed it is necessary to consider more closely some of the transformations mentioned in the previous chapter.

The solvolysis of camphene hydrate esters (IV) to *iso*bornyl esters (V) was studied by Meerwein and his collaborators (1). It was shown to be a reversible equilibrium strongly favouring the *iso*bornyl ester. It was catalysed by strong acids, and, as would be expected in a rate-determining ionisation, it was accelerated by solvents with high dielectric constants. The rates varied also with the esters in the following order: sulphonate > bromide > chloride > trichloroacetate > *m*-nitrobenzoate—that is, approximately in the order of strength of the corresponding acids. The rate of chloride exchange, as shown isotopically, is *much* greater than the rate of solvolysis. These transformations may be written in terms of bare ions as shown opposite. This representation must be inadequate since the ion (VI), for instance, has lost its stereochemical individuality and the product might be expected to be the more stable bornyl ester (VII). However, accepting one of the proposed methods of retaining stereochemical identity—that is, by presupposing some sufficient degree of concertion—the problem is rationalised (9).

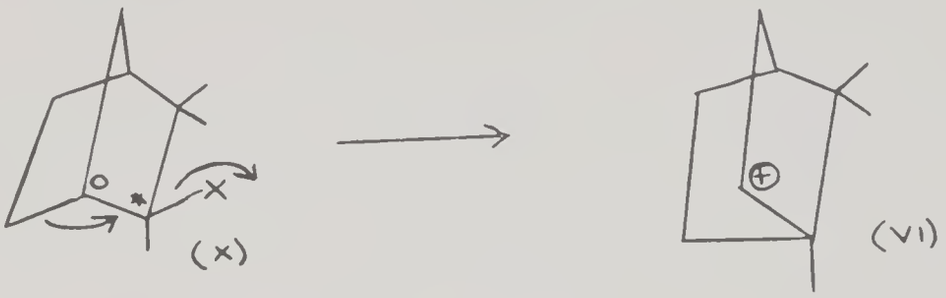
The change (IV) $\longrightarrow$ (VIII) $\longrightarrow$ (IX) $\equiv$ (VI) may be condensed into

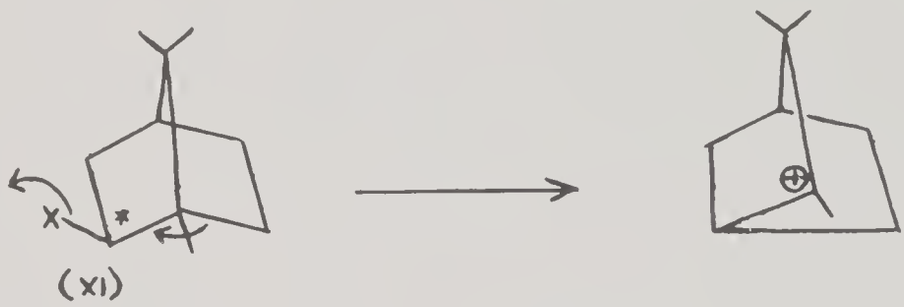

X
(IV)
X
(V)
X
X
(IV)
(VIII)
(IX)
X
(VII)
X
(V)
(VI)

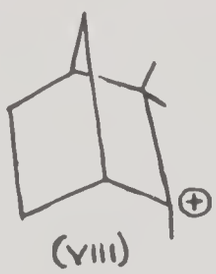
the expression (X). At the carbon atom marked with the asterisk a transformation analogous to bimolecular substitution may be considered to have taken place. In this the approaching substituent is the bond-forming electron pair, whilst X is the usual departing group. Since this reaction is reversible, it is stereospecific in both directions each involving a Walden inversion at the asterisked carbon atom.

In (X) the carbon atom indicated with the circle is that represented as bearing a positive charge in (VI) and in the equivalent (IX). Now, since all stages are reversible, it is possible to represent the solvolysis of (V) as in (XI). Here again, bimolecular substitution can be considered as having taken place, with Walden-type inversion at the asterisked carbon atom. This requires that the stereochemical integrity at the asterisked carbon atom be maintained in both directions. Now, since the asterisked carbon atom in (XI) is the circled carbon atom in (X), it necessarily follows that during the conversion of (IV) to (V) the stereochemical individuality of *both* relevant centres has been maintained. That is, the entire reaction is stereospecific. It is of particular importance to note that such stereospecificity is attained because the equivalent of bimolecular substitution at the relevant carbon atom *is* possible. When the configuration of the solvolysed group is *not* suitable, as in (VII), alternative paths are sought.

With this clarified it is now possible to interpret the complex sequence of changes from α-pinene to bornyl chloride to camphene


(X)
(VI)


(XI)


(VIII)

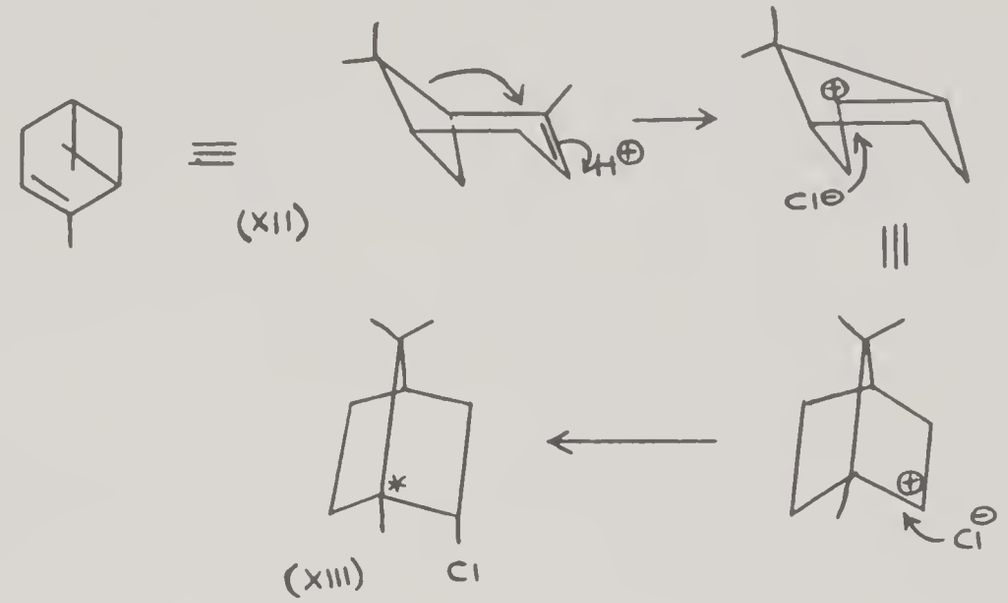
(and camphene hydrochloride) and, as just described, to *iso*bornyl chloride.

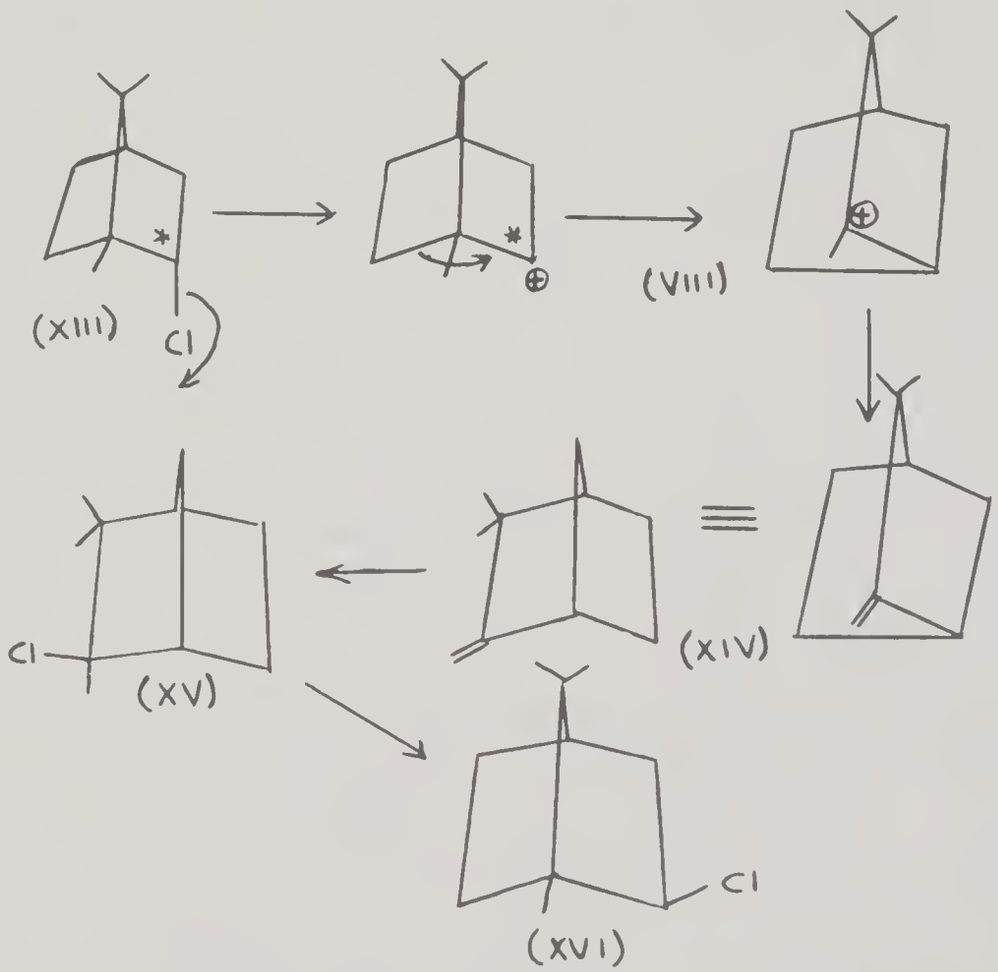
The protonation of the double bond in α-pinene (XII) is followed by a Wagner shift. As the four-membered ring cleaves, the anion approaches from the side opposite to the departing electron pair; followed to completion the product is bornyl chloride (XIII). Now the conversion of bornyl chloride (XIII) to camphene (XIV) through the ion (VIII) cannot be a concerted process since the necessary geometry does not obtain and the reaction is, therefore, correspondingly sluggish. This concerns the carbon atom bearing the halogen. At the asterisked carbon atom at which the charge may be generated, eventual participation will result in the formation of the ion (VIII). Participation, however, cannot occur in the rate-determining step because of the rigid and unfavourable geometry. The product, with loss of a proton, will be camphene. The derived hydrochloride (XV) will be transformed, as already described, to give *iso*bornyl chloride (XVI).

Some idea of the relative stabilities of bornyl and *iso*bornyl may be obtained from the fact that the equilibrium mixture contains significant amounts of the less stable *iso*bornyl chloride (1,44).

In the above discussion it has been stated that participation aids solvolysis, and that where this participation is not geometrically possible the process is correspondingly more difficult. Hughes, Ingold, and their collaborators use the terms "synartetic acceleration" and "synartetic ion" when referring to participation of phenyl or alkyl groups, the terms being restricted to cases involving shared σ-electrons. It does not thus extend to cover all examples of neighbouring group participation or "anchimeric acceleration," the term used by Winstein and his colleagues.

This group of workers has investigated the anchimeric acceleration of solvolysis of the halides and aryl sulphonates of the simpler related norbornyl derivatives as well as some others (10). It has

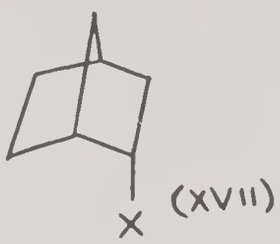

(XII)
ClΘ
(XIII)
Cl
Cl


(XIII)
Cl
(VIII)
Cl
(XV)
(XIV)
Cl
(XVI)

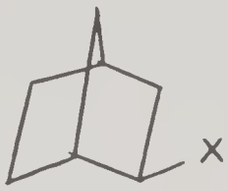
been found that the bornyl and *endo*norbornyl (XVII) derivatives have a rate of solvolysis essentially identical with that of *cyclo*hexyl derivatives. However, as compared with the latter *exo*norbornyl derivatives (XVIII) solvolyse 516 and *iso*bornyl 3.5×10^5 times faster (or 350 and 2.5×10^5 faster than the corresponding epimers). Even when allowance is made for release of steric strain (11) these results provide tangible evidence that carbon participation really occurs (and of its magnitude) in, say, the conversion of (XV) to (XVI), but *not* of (XIII) to (XV).

The transformations shown have been represented as a single process, concerted or otherwise, involving, in the potential energy diagram, a single peak at a transition state. If there is a bridged, synartetic ion this, being more stable than either of the classical ions from which it is derivable, will represent a "well" in the potential energy diagram, the depth of the well being a measure of the stability of the bridged ion. Evidence for the existence of such ions in terpene chemistry has been accumulating in recent years.

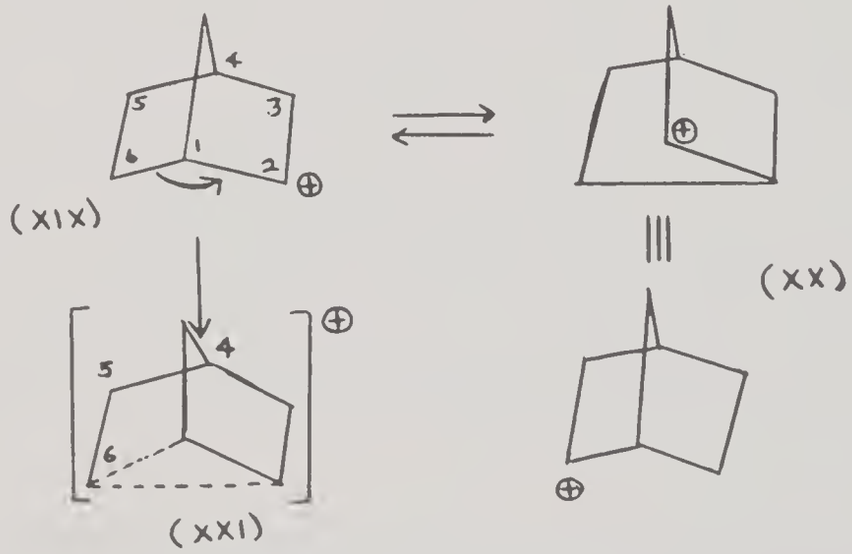
The solvolysis of *endo*norbornyl arylsulphonates proceeds in glacial acetic acid, aqueous acetone and in aqueous dioxan to give, exclusively, the corresponding *exo* derivative. This isomerisation, in the optically active (12) derivative, was attended with complete racemisation, and it was also shown that the racemisation was an intrinsic part of the solvolysis and not a racemisation of the ester *prior* to solvolysis. The results also excluded the possibility that an SN_2 displacement of the ester took place to give the *exo* derivative, followed by a rapid solvolysis of the latter. The racemisation, therefore, takes place in the cation. It must involve *at least* Wagner-Meerwein rearrangement or a shift from C_6 to C_2 (2 : 6 shift) of hydrogen. It may be represented as an equilibrium between the mirror-image ions (XIX) and (XX) or as the bridged ion (XXI) which has a plane of symmetry through C_4, C_5, and C_6. The solvolysis of the optically active isomeric *exo* derivatives (12) is more complex, since the rate of racemisation and rate of solvolysis are not the same. The data showed that there was no *exo* $\longrightarrow$ *endo* conversion. The racemisation in excess of that caused in the aryl sulphonate itself (possibly by an ion-pair



(XVII)



(XVIII)



(XIX)

(XX)

(XXI)

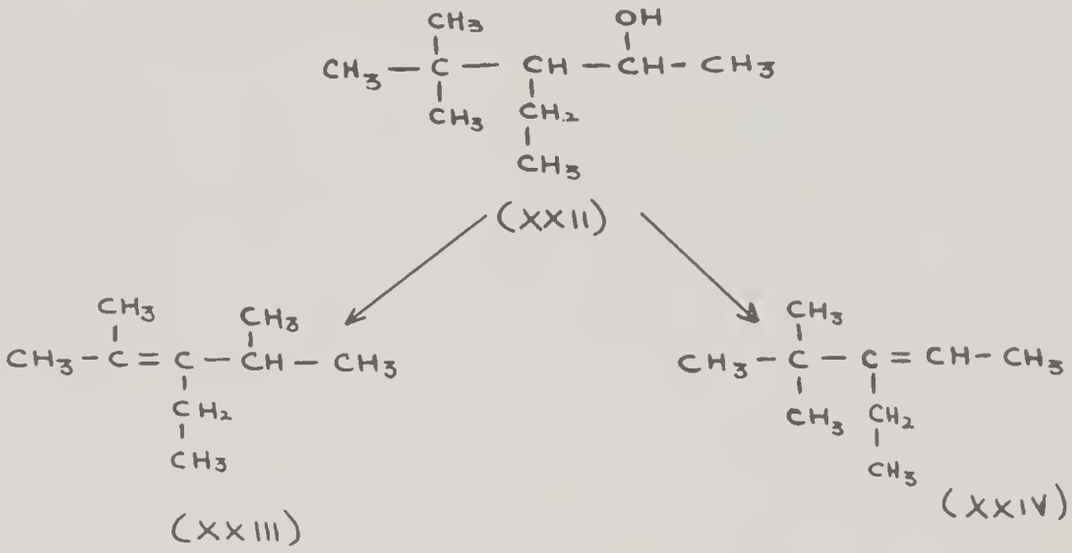
(41) mechanism) increased in the order: acetolysis to ethanolysis to hydrolysis. Again, there are several possibilities in mechanistic detail, including 2 : 6 and 2 : 3 hydrogen shifts.

It must be mentioned that the evidence for 1 : 3 hydrogen shifts (equivalent to the above 2 : 6 shifts) in general is only gradually becoming clearer.* One of the more compelling examples of a 1 : 3 shift in open chain compounds is, perhaps, that of Mosher and Cox (13) who dehydrated 4 : 4-dimethyl-3-ethyl-2-pentanol (XXII) and obtained 57% (XXIII) and 43% (XXIV), the former involving either a 1 : 3 methyl shift or a long series of 1 : 2 shifts at least one step of which requires the formation of a secondary carbonium ion from a tertiary. Carbon migration, when a carbon–carbon bond is favorably oriented, is alternative to hydrogen shifts. But migration (Nametkin) in the *iso*bornyl cation is known to be slow (14). Other qualifications therefore become necessary to account for almost complete formation of the *exo* derivative. Again, the intervention of the bridged ion (XXI) has been invoked. The bridged ion postulated here (22) parallels the earlier (15) suggestion of Nevell, Salas, and Wilson of a resonance cation (XXV) derived from camphene hydrochloride.

Whilst evidence is not entirely compelling as yet, such concepts explain much: the formation, in solvolyses, of *iso*bornyl and camphene hydrate derivatives (and not those of the epimeric bornyl and methyl camphenilyl), the formation of traces of tricyclene, and the observed solvolysis rate sequences.

The above considerations are in effect a minimum explanation. It was shown by the use of isotopic (C^{14}) carbon that the transformations examined were far more complex (16). In one investigation C^{14}-labelled *exo*- and *endo*norbornyl derivatives substituted at C_2 and C_3 were used. The *p*-bromobenzenesulphonates were solvolysed in alcohol, acetic acid, and formic acid. Under the scheme so far considered the probability of reaction at C_1 and C_2 in the

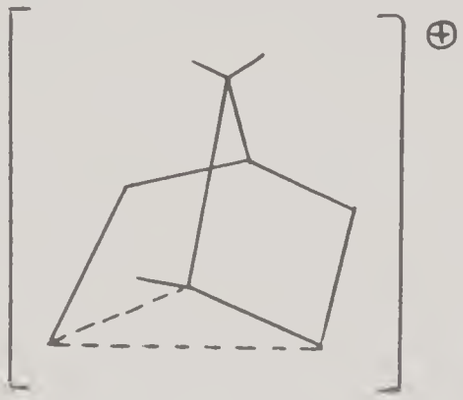
*The occurrence of *trans*-annular hydrogen transfer has been rigidly established, of course, by the work of Cope (45) and of Prelog (46).



(XXII)

(XXIII)

(XXIV)

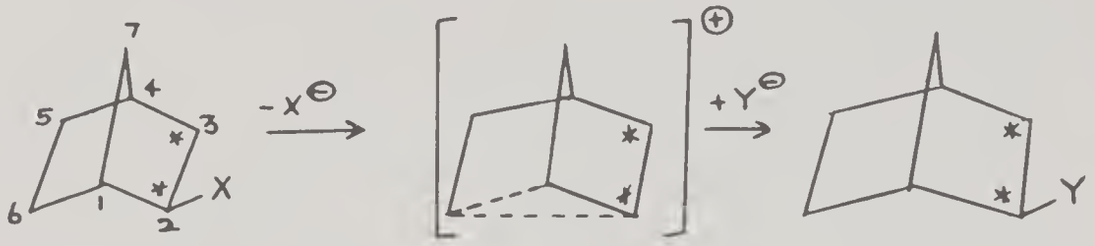


(XXV)

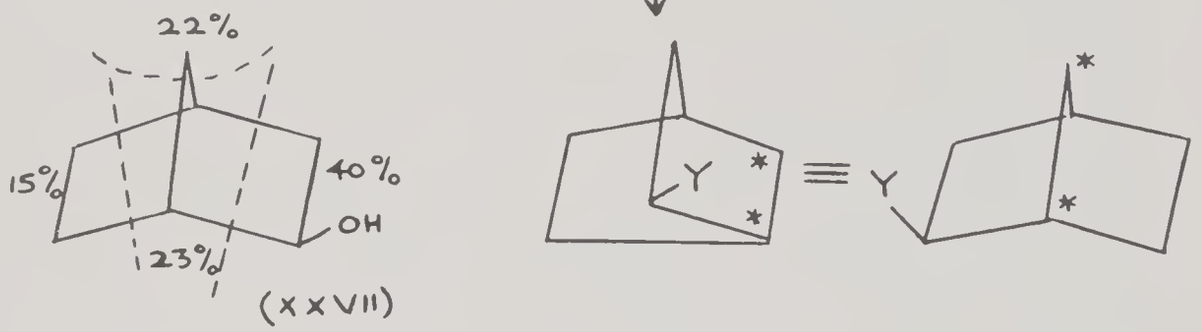
bridged ion (XXVI) is equal (ignoring isotope effects) and so a maximum of 50% migration of activity from C_2 and C_3 to C_1 and C_7 is possible, with no possibility of migration into the C_5 and C_6 positions. Indeed, no combination of 1:2 shifts of carbon or hydrogen could introduce activity at these points. However, such migration does take place and a typical analytical result is shown in (XXVII); 2:6 shifts, or their equivalent, must therefore occur.

Two alternative formulations have been proposed. In one a contribution from the ion (XXVIII), a non-classical nortricyclonium ion, to the process is envisaged. In the other an equilibrium between the ions (XXIX), (XXX), and (XXXI), all bridged, is supposed. Inter-conversion requires hydride shifts (12,18). The essential difference between these formulations is that of whether (XXVIII) is a true intermediate corresponding to a minimum in the potential energy curve or whether it is merely a transition state. At present no distinction can be made.

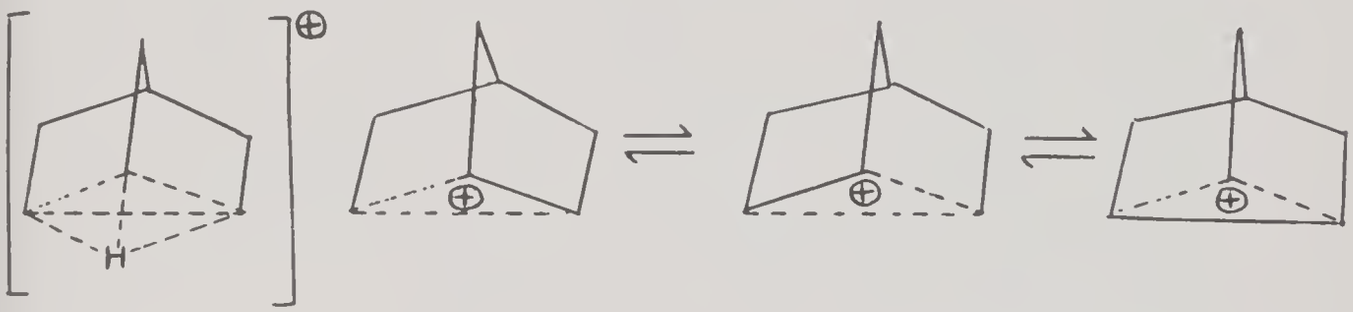
With these studies in mind the more complex processes underlying the mechanism of the racemisation of a true monoterpenoid, camphene (16,17), may be better understood. It has been shown that optically active camphene racemises by at least two simultaneous processes in the presence of hydrated titanium dioxide, pyruvic acid, or aniline hydrochloride. One of these involves, probably,



(XXVI)



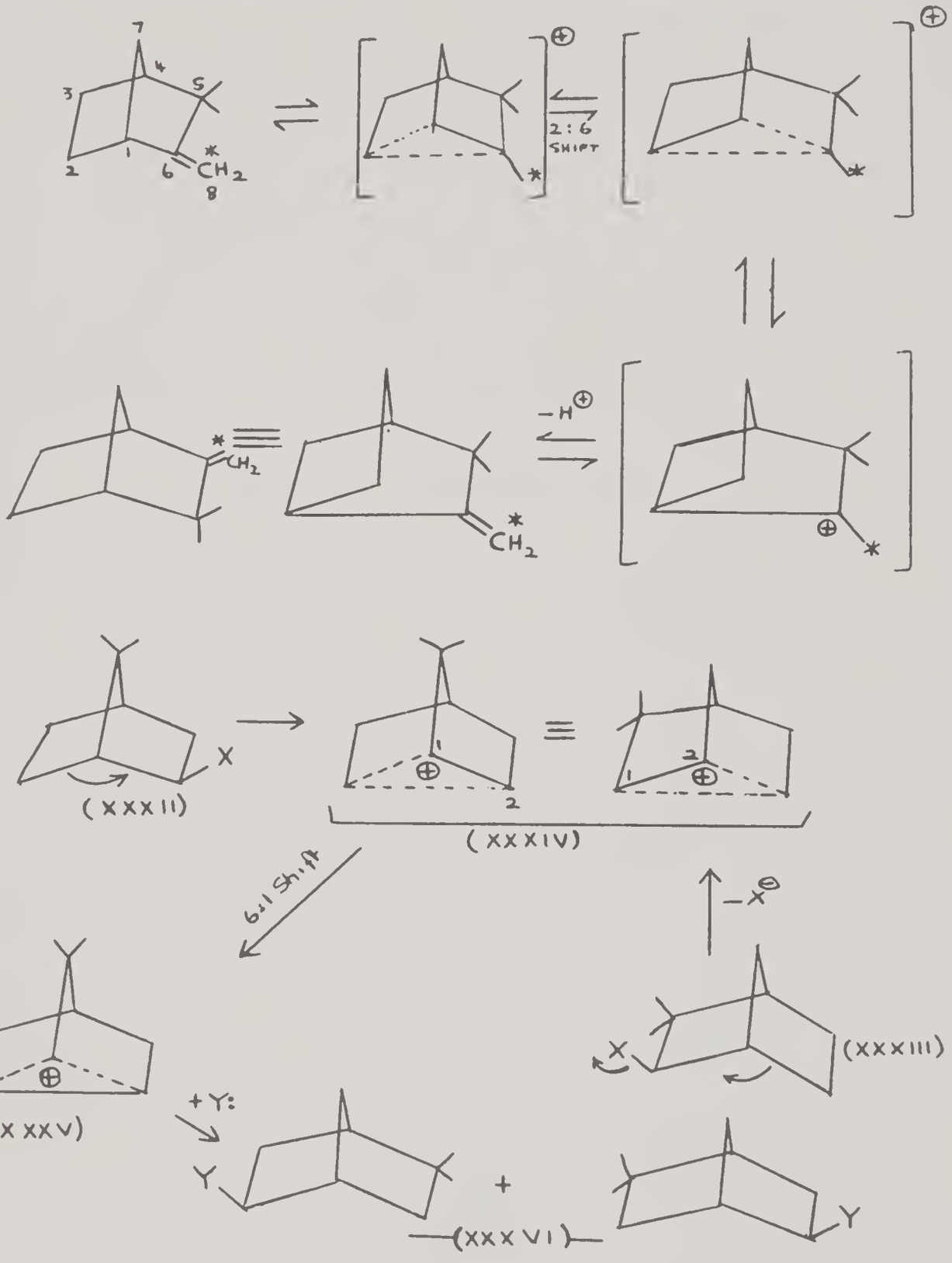
(XXVII)



(XXVIII) (XXIX) (XXX) (XXXI)

shifts similar to those described above and does *not* involve movement of the C_8-labelled carbon atom. The other process involves a normal Nametkin shift; in this the labelled carbon atom becomes distributed amongst the side-chain carbon atoms.

In these reactions involving a 2:6 hydride shift the question arises as to whether this occurs in competition with, or subsequent to, carbon bridging. For instance, in the solvolysis of norbornyl bromobenzenesulphonate (16) the extra "shuffling" of the labelled carbon decreased in the solvent sequence formic acid to acetic acid to aqueous acetone. Since this is the order of increasing nucleophilicity of solvent it has been interpreted (19) as meaning that hydride shift occurs subsequent to carbon participation, i.e., in the bridged ion. Further, and impressive, evidence has been obtained in a study of the *apoiso*bornyl (XXXII) and *exo*camphenilyl (XXXIII) systems. These are related through a 1:2 shift to the common bridged ion (XXXIV). In this, addition at C_1 gives (XXXIII) and at C_2, (XXXII). A 6:1 hydrogen shift (again equivalent to an acyclic 1:3 shift) in (XXXIV) leads to the β-fencho*iso*camphoryl bridged cation (XXXV) which then, by addition at C_2 or C_6, gives racemic β-fencho*iso*camphoryl derivatives (XXXVI). If hydrogen shift takes place *after* carbon participation, that is, in the ion (XXXIV), then the same amount of shift must occur irrespective of whether the starting material is (XXXII) or (XXXIII). Further, if it *is* a subsequent step, then by shortening the life of the ion (XXXIV) with a powerful nucleophilic solvent it should be possible to eliminate hydride shift or at least reduce it. Both these predictions were realised. In the solvolysis of the bromobenzenesulphonates in acetic acid of both (XXXII) and (XXXIII) about 49% of the β-fencho*iso*camphoryl derivative was obtained. By solvolysis in thionyl chloride at 0° none was found. Similar conclusions were reached (20,21) on an examination of the solvolysis rates of nopinyl esters which are simpler analogues of pinene derivatives. Similarly, 2:6 hydrogen shifts have been postulated (23) in the dehydration of β-fenchol and (12,24) in the action of nitrous acid


2:6 SHIFT
(XXXII)
(XXXIV)
6:1 Shift
(XXXV)
(XXXIII)
(XXXVI)

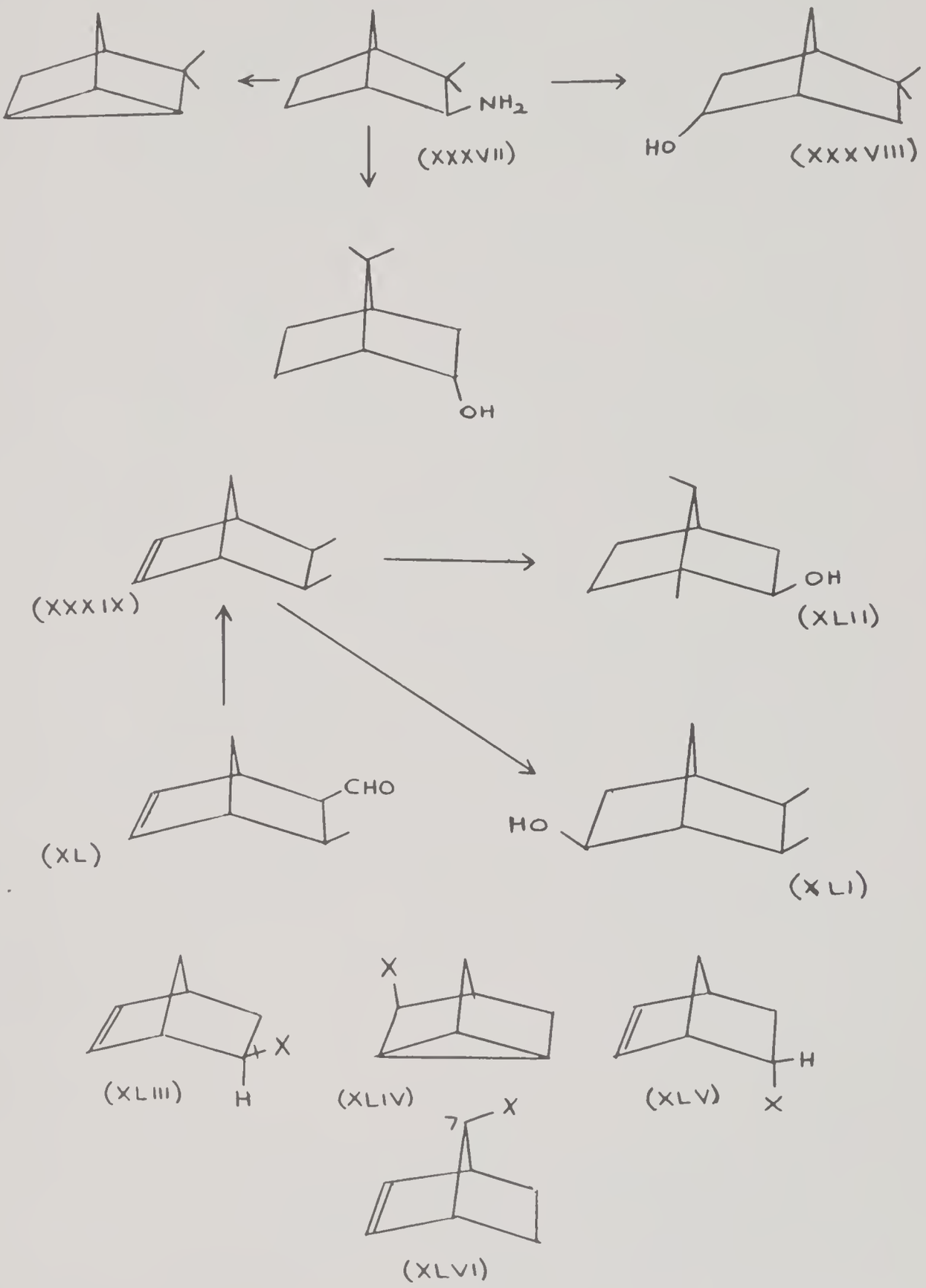
on camphenylamine (XXXVII). In this reaction some β-fenchoisocamphorol is obtained (XXXVIII) and it is significant that the amount of the latter decreases with the mildness of the conditions.

An interesting analogous reaction has been performed on *p*-santene (XXXIX). This is not a natural product, but is obtained by the Wolff-Kishner reduction of (XL), itself obtained by the condensation of crotonaldehyde with *cyclo*pentadiene (26). In the reaction with hydrogen chloride (followed by hydrolysis with lime-water) the main product was (12,25) the alcohol (XLI) formed by simple addition. In acetic–sulphuric acid some α-santanol (XLII) is formed and when 99% formic acid is used this is essentially the only product.

THE NORBORNENYL SYSTEM

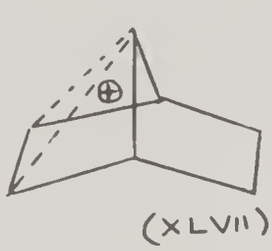
While the substances to be briefly discussed in the following section are not terpenoids, their basic skeletons are the same. They are included because of their great interest, and because their study leads to a greater understanding of the intimate chemistry of the related terpenoids.

Investigation of the solvolysis rates of unsaturated norbornyl derivatives, as compared with the corresponding saturated derivatives, has produced (27–29) very interesting results. The acetolysis of the *p*-bromobenzenesulphonates of (XLIII), (XLIV), and (XLV) to give the acetate of (XLIV) (in 80% yield) proceeded in the rate order of 7000 : 2000 : 1. This indicated a very substantial driving force in (XLIII) which has the proper configuration for delocalisation of the π-electrons of the double bond in the rate-determining ionisation. In (XLV) this delocalisation must occur *subsequent* to the ionisation. Even more striking is the difference in the first-order rate constants for the acetolysis of (XLIII) toluenesulphonate and that of *anti*-7-norbornenol (XLVI). This difference is a factor of 25, even though (XLIII) itself is already strongly accelerated. The extraordinary potency of the acceleration is demonstrated (30) by a comparison of the solvolysis rate of (XLVI) toluenesulphonate as against that of the saturated analogue, where stabilisation of a (non-

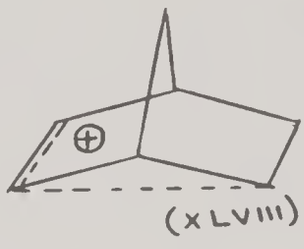

NH2
(XXXVII)
HO
(XXXVIII)
OH
(XXXIX)
OH
(XLII)
CHO
(XL)
HO
(XLI)
X
H
(XLIII)
X
(XLIV)
H
X
(XLV)
X
(XLVI)

planar) carbonium ion at C_7 is geometrically very difficult. The rates are as $10^{11}:1$. This reactivity has been attributed to the overlap between the vacant *p*-orbital on C_7 and those of the 2:3 linkage. In fact the 2–7 (or 3–7) distance in the 7-norbornenyl cation is less than the 3–5 distance in the cation derived from (XLIII). Both of these contain what is termed the homoallylic system (31). The 7-norbornenyl cation may be represented as (XLVII), and it reacts stereospecifically with the solvent with complete retention of configuration. It may be compared with (XLVIII), the corresponding ion from (XLIII). The bromination of norbornylene has been studied (32). With both *N*-bromosuccinimide and bromine norbornyl bromide a saturated bromo compound (XLIX) can be obtained. In the presence of excess pyridine the latter is the only product. Reaction of this bromide with magnesium and decomposition affords the saturated hydrocarbon. The mechanism of this bromination process is uncertain but if, as seems probable, positive bromine is the active agent the transformation may be represented as shown opposite. A similar reaction carried out on *endo*dehydronorbornyl derivatives (L) also gives (XLIX). This process is similar to that involved in the formation of *i*-cholestane (3:5-*cyclo*cholestane) (LI) derivatives from those of (LII) cholesterol (7,33), and of *cyclo*propylmethyl compounds (LIII) from certain allyl derivatives (LIV) (34). These are further examples of homoallylic behaviour. Others studied (35) include certain chlorination products of norbornylene.

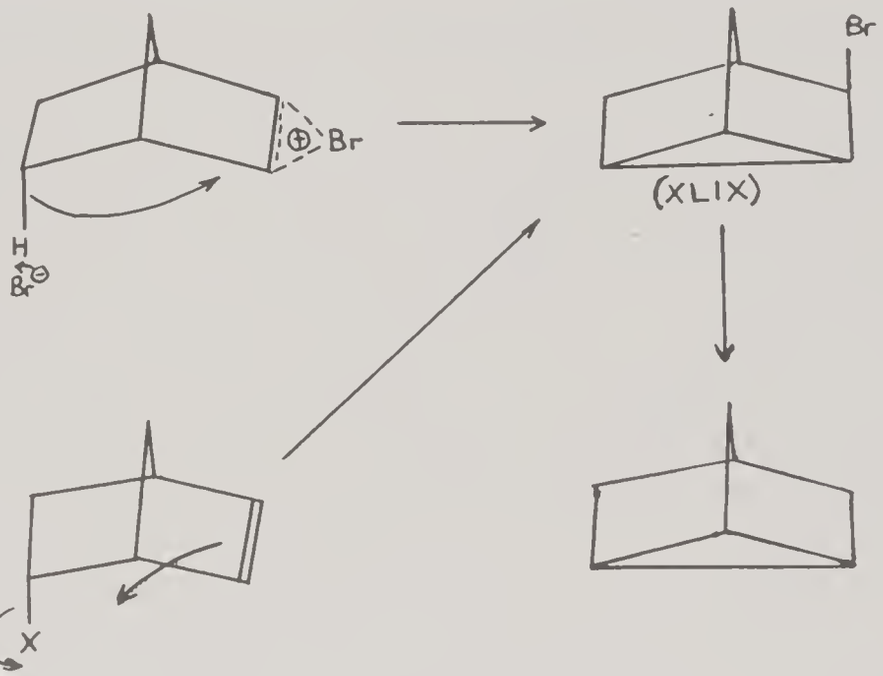
Extension of such systems has been realised (36) in the addition of suitable reagents to the doubly unsaturated bi*cyclo*heptadiene

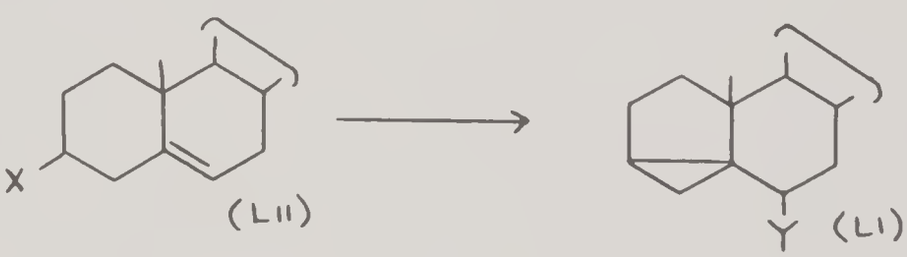


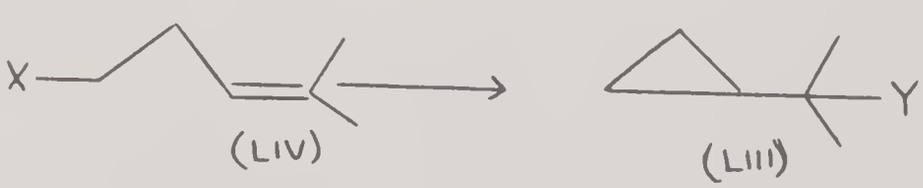
(XLVII)



(XLVIII)



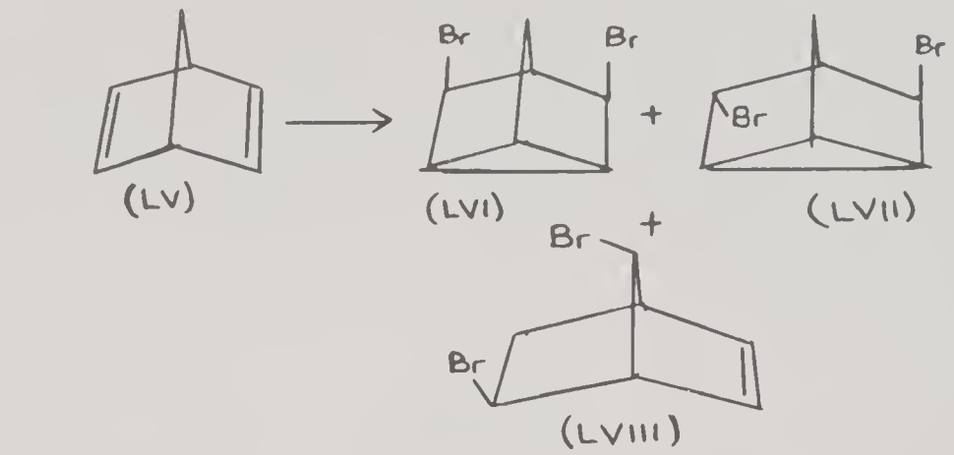


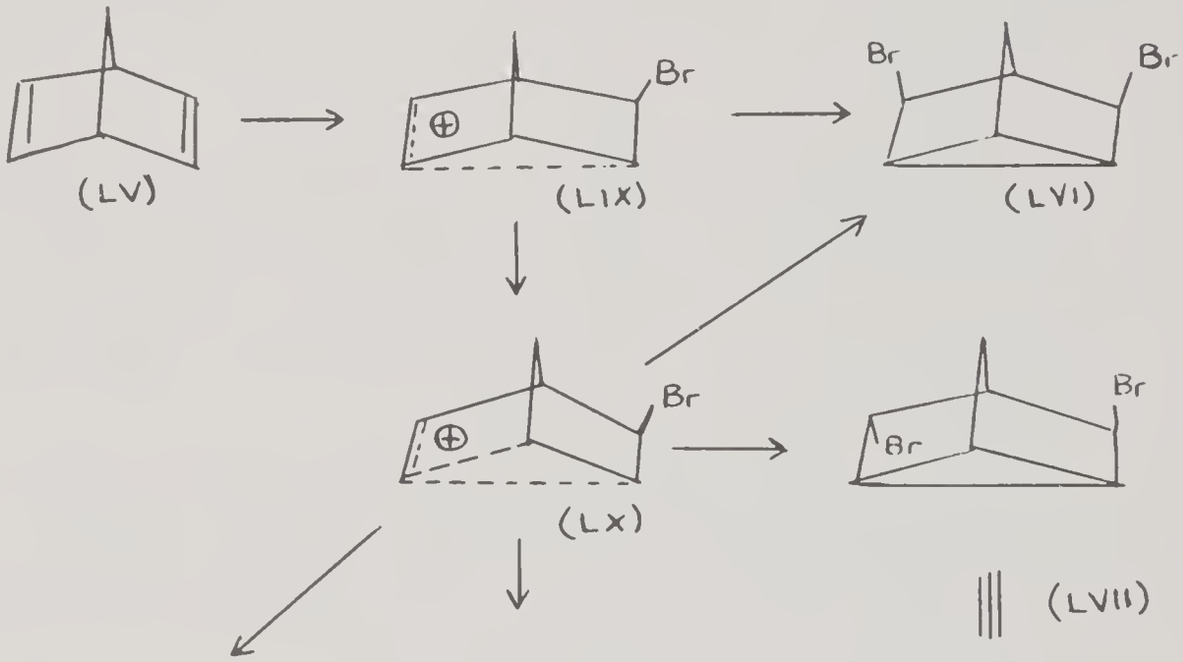


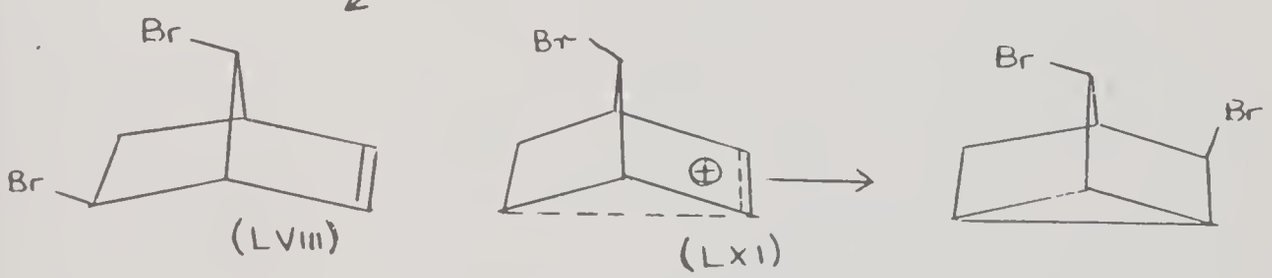
(LV). One example is the addition of bromine which gives (LVI), (LVII), and (LVIII). The results of these additions have been interpreted in the following way. Addition leads first to the homoallylic bridged ion (LIX). This may react, without rearrangement, to give (LVI); or it may rearrange to give the bridged species (LX) and (LXI). These may react further, as shown. All the additions are presumed to be stereospecific except the direct conversion of (LX) to (LVI) and (LVIII).

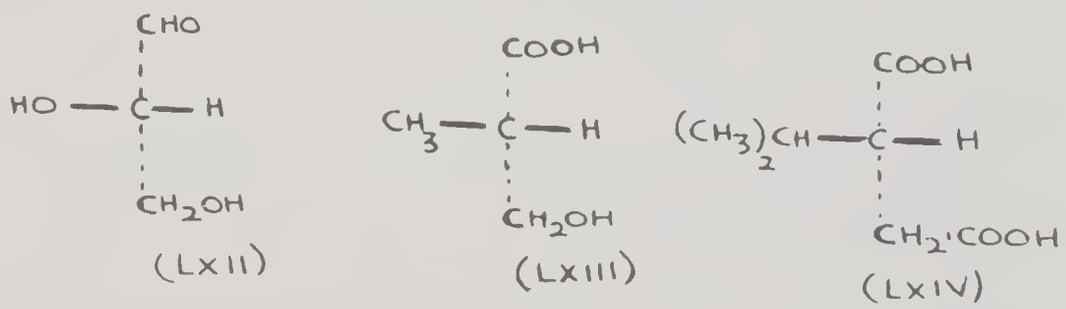
THE ABSOLUTE CONFIGURATION OF THE MONOTERPENOIDS

Many of the mono- and bicyclic monoterpenoids have been correlated with L-glyceraldehyde (LXII), and so with the sugars. This has been made possible largely by the work of Fredga (38). By the method of "quasi-racemates" he has shown that (–)-methylsuccinic acid (LXIII) and (–)-*iso*propylsuccinic acid (LXIV) are to be represented as shown. These are products frequently obtained by the oxidative degradation of the monoterpenoids. With this and the known interrelationships from other chemical transformations collected by Hückel (39) a list of representative terpenoids has been


Br
Br
Br
Br
+
+
Br
(LV)
(LVI)
(LVII)
(LVIII)


Br
Br
Br
Br
Br
(LV)
(LIX)
(LVI)
(LX)
(LVII)


Br
Br
Br
Br
Br
(LVIII)
(LXI)


CHO
HO — C — H
CH2OH
(LXII)
COOH
CH3 — C — H
CH2OH
(LXIII)
COOH
(CH3)2CH — C — H
CH2·COOH
(LXIV)

compiled by Birch (40). Some of these are shown opposite, and include (+)-camphene (LXV), (+)-camphor (LXVI), (+)-fenchone (LXVII), (+)-α-pinene (LXVIII), (+)-α-terpineol (LXIX), (+)-limonene (LXX), (−)-carvone (LXXI), (−)-car-4-ene (LXXII), (−)-menthone (LXXIII), (+)-pulegone (LXXIV), (+)-citronellal (LXXV), and (+)-D-methylsuccinic acid (LXXVI).

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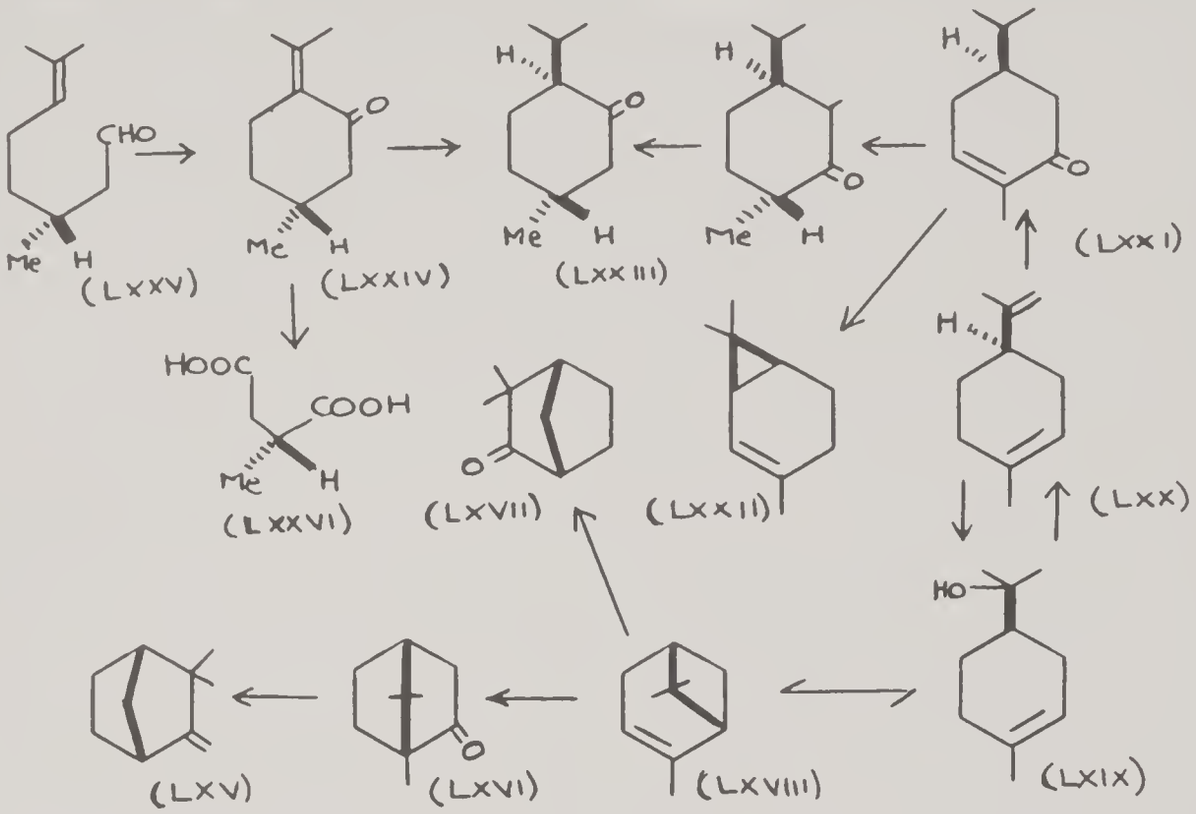

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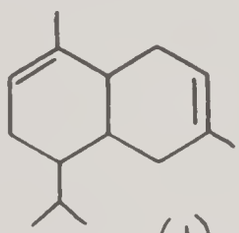
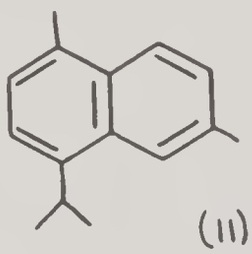
THE SESQUITERPENOIDS: I

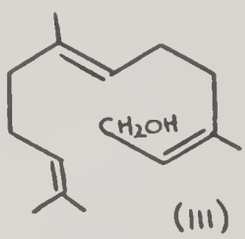
Although the study of the sesquiterpenoids was begun in the early years of the nineteenth century, it was only after about 1920 that serious progress began to be made. Whilst Wallach (1) believed that the sesquiterpenoids, like the monoterpenoids, were built up from isoprene nuclei, the nature of the union was quite unknown. In 1921 Ruzicka and Meyer (2) discovered that a bicyclic hydrocarbon, cadinene (I), gave the naphthalenic hydrocarbon cadalene (II) on dehydrogenation by heating with sulphur. The constitution of the latter was established by synthesis. This transformation was of particular importance because cadalene contained all the carbon atoms present in the original hydrocarbon. Furthermore, the arrangement of the isoprene nuclei was just that which had been found in the alcohol, farnesol (III), the constitution of which was known at that time. This dehydrogenative procedure was an extension of a technique used by Vesterberg (3) in the chemistry of abietic acid. It was soon applied further, and in 1922 (4) Ruzicka and his collaborators found that dehydrogenation of eudesmol (IV) and selinene (V) gave a new hydrocarbon, eudalene (VI). This contained, however, only fourteen of the original carbon atoms and it was correctly concluded that the eliminated carbon atom was a quaternary methyl group. Since the structure (VII) cannot be constructed from three isoprene units, the alternative (VIII) was accepted as being the carbon skeleton of these substances. The assumption was correct, and the general conclusion that the basic structures of the sesquiterpenoids should be derivable from isoprene units still holds largely true today. An exception is eremophilone (IX) which is, in fact, based on the alternative structure



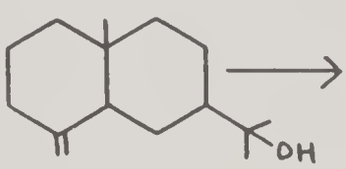
(I)



(II)



(III)



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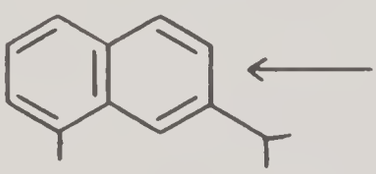
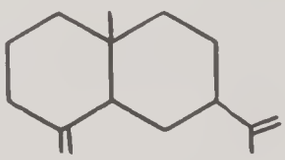


(VI)



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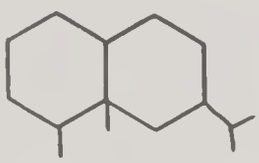
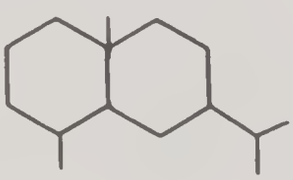
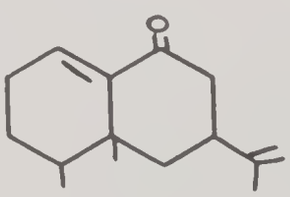


(VII)



(VIII)



(IX)

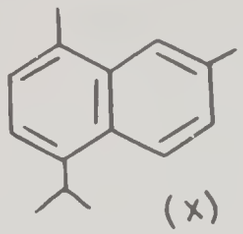
(VII). Its formation, as discussed later, is believed to involve methyl migration at a fairly late stage rather than a radically different process of biogenesis. More recently, a further naphthalenic-type hydrocarbon (X) has been obtained from the alcohol carotol (5) (page 310) by Sorm and Urbanek.

It had been noted for very many years that certain essential oils, when distilled, oxidised, or even subjected to mild treatment with acids, developed a blue colour. Many of the sesquiterpenoids gave similar blue substances when dehydrogenated, and the blue colour was attributed to the presence of a small group of hydrocarbons. The name "azulene" was applied to the oils by Piesse in 1804 and has been transferred to the parent hydrocarbon (XI) of this series of compounds. Those azulenes which were first obtained from natural sources were given trivial names, but as their identity with other hydrocarbons was established the superfluous names were discarded. The majority (of this group of substances) at the present time, have a carbon skeleton based on guaiazulene (XII); but some other skeletal types, such as vetivazulene (XIII) and zierazulene (XIV), are also known.

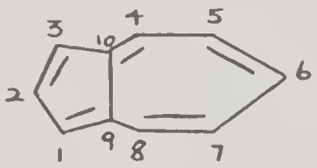
The techniques used in dehydrogenation to obtain the basic hydrocarbon from a sesquiterpenoid are such that the final product need not contain exactly the original skeleton. The elimination of an angular methyl group, already mentioned, is an instance of this. Apart from sulphur, selenium and palladised charcoal are common reagents, being used in the region of 250–330°. Of these, selenium, possibly because of the somewhat higher temperature used, is most prone to induce rearrangements. Zinc, too, has been employed (6), but even more drastic rearrangements may then occur.

In lactonic substances the usual behaviour on dehydrogenation is the loss of carbon dioxide, giving thereby a hydrocarbon containing only fourteen carbon atoms. A common example of such an end product is the azulene chamazulene (XV). This is, therefore, the second way in which a carbon atom may be eliminated during dehydrogenation.

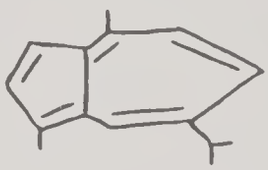
If selenium is used to dehydrogenate guaiol (XVI), an isomer of guaiazulene (XII) is obtained, known as Se-guaiazulene (XVII). In



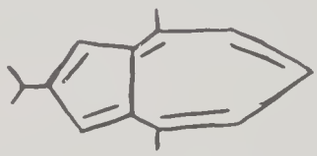
(X)



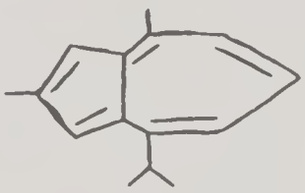
(XI)



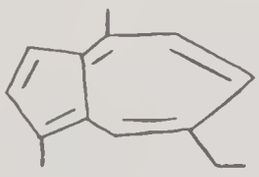
(XII)



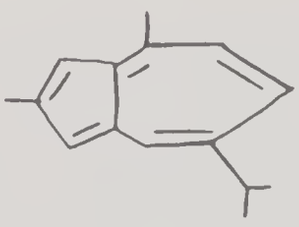
(XIII)



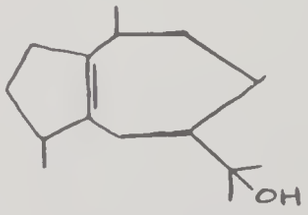
(XIV)



(XV)



(XVII)



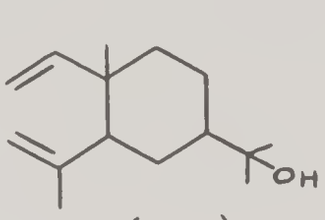
(XVI)

this case no elimination has taken place, but the hydrocarbon obtained by dehydrogenation differs in skeleton from its precursor. Yet more deceptive and complex transformations are possible. For instance, when the substance contains suitably placed ethylenic linkages, cyclisation may precede dehydrogenation. Thus, elemol (XVIII), for example, gives some eudalene. Zingiberene (XIX) gives cadalene, with cyclisation, but on the other hand, bisabolene (XX) does not. Both cyclisation and rearrangement may occur, and elemol gives, together with the eudalene, some vetivazulene. Rearrangement is particularly to be expected when aromaticity is blocked by, for instance, a methyl group. If a substituent α-to this block is eliminated more readily than the methyl group itself, a positive charge is provided next to the bridge, and migration of the bridging bond to the adjacent position becomes likely. Thus, dihydro*cyclo*pyrethrosin acetate (XXI) (page 232) (7) gives chamazulene, with loss of carbon dioxide, by migration of the bridging bond to the position previously occupied by one acetoxyl group.

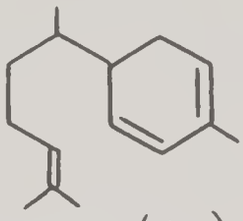
The sesquiterpenoids are most readily classified on the basis of their skeletons, when, apart from a few acyclic derivatives, they may be divided into cadalene, eudalene, or azulene types, and some associated monocyclic derivatives. There are, in addition, a number of important substances which cannot be here included. They do not, as a rule, give informative hydrocarbons on dehydrogenation, and they have provided some of the most complex and subtle of the structural problems to be found in this group of compounds.

THE ACYCLIC SESQUITERPENOIDS

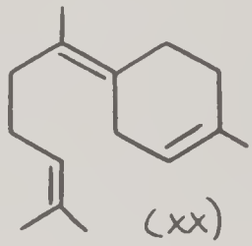
Farnesol (XXII) is the most important substance in this small group. It is fairly widely distributed in nature and has been found in citronella oil, rose oil, Seville orange oil, and many others. It was investigated by Kerschbaum (8), who elucidated its structure, and it was, in fact, the first sesquiterpenoid structural problem to be solved. Digestion with potassium carbonate of the related aldehyde, farnesal, gives by addition and dealdolisation, dihydro-



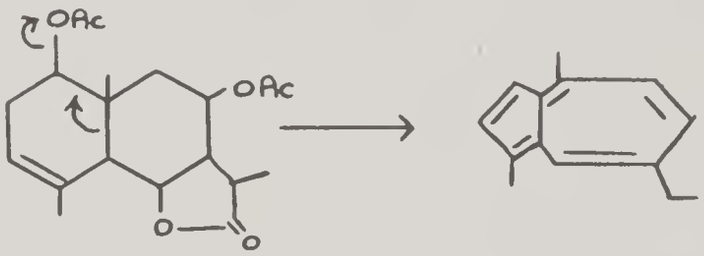
(XVIII)



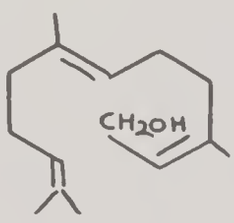
(XIX)



(XX)



(XXI) (XV)

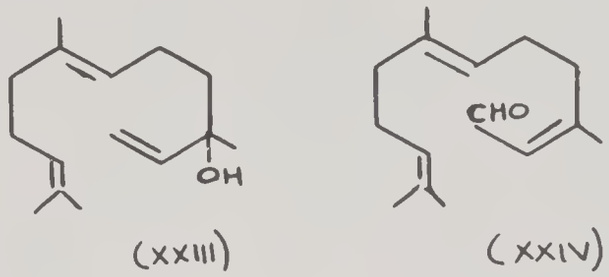


(XXII)

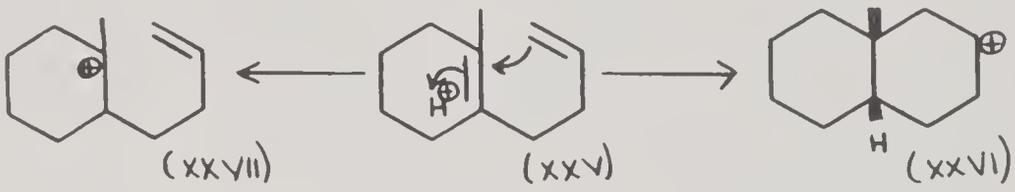
ψ-ionone (geranyl acetone) (page 44) (9). One of the possible dehydration products, β-farnesene, has been found in oil of hops, ginger oil, etc. (10). Since it is possible to convert nerolidol (see below) into farnesol derivatives, and since nerolidol has been synthesised from geraniol, the centre double bond in farnesol is presumably *trans*; this is probably also true of the terminal conjugated double bond in farnesal (where equilibration is possible), though not necessarily in natural farnesol.

The alcohol **nerolidol** (XXIII) is found in neroli oil from the flowers of the bitter orange and bears the same relationship to farnesol as does linaloöl to geraniol. Thus, in a way parallel to linaloöl (which gives citral), nerolidol gives (with chromic acid) farnesal (XXIV), a process involving an anionotropic rearrangement. It may be prepared from geranyl acetone by condensation with acetylene and partial reduction (cf. linaloöl, page 42).

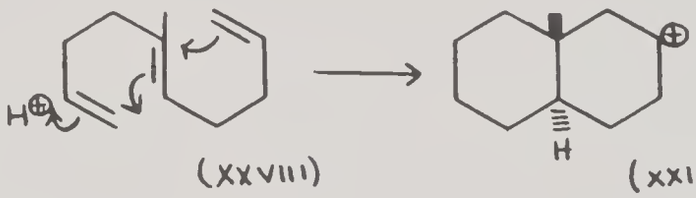
Recently a number of interesting cyclisations on derivatives of farnesol have been carried out (10). As an example some of the investigations on farnesenic (farnesic) acid may be quoted. These were undertaken in an attempt to discover whether the cyclisation of polyenes was a concerted process or not. Thus, whilst ring closure of the monocyclic 1:5 diene (XXV), by a concerted *trans* attack on the cyclic double bond of a proton and the π-electron of the other double bond, should lead, through the ion (XXVI), to a *cis*-octalin derivative, a non-concerted cyclisation through the carbonium ion (XXVII) (or equivalent) would be expected to give a mixture of *cis*- and *trans*-octalins. On the other hand, concerted cyclisation of the triene (XXVIII) should lead, through the ion (XXIX), to a *trans*-octalin. These considerations are of importance with regard to triterpenoid chemistry in particular, and it should be noted that should the centre double bond have the unsaturated substituents *cis* then the product of concerted cyclisation will be a *cis*-octalin. This will be better appreciated by inspection of models (11). Attempts to effect such stereospecific cyclisation using farnesenic acid (XXXVI) have not been very successful. Thus, with boron trifluoride–ether in benzene below 5° the monocyclic acids (XXX) and (XXXI) were obtained. These were then transformed by the same reagent at 40° into the *cis*-octalins (XXXII),



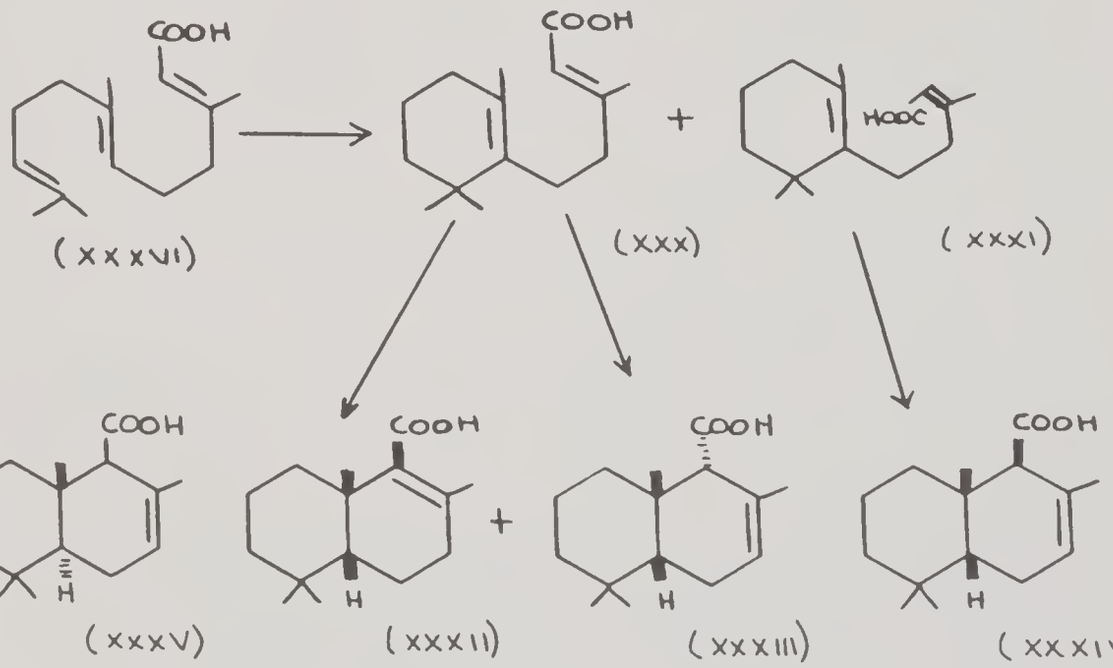
(XXIII) (XXIV)



(XXVII) (XXV) (XXVI)



(XXVIII) (XXIX)



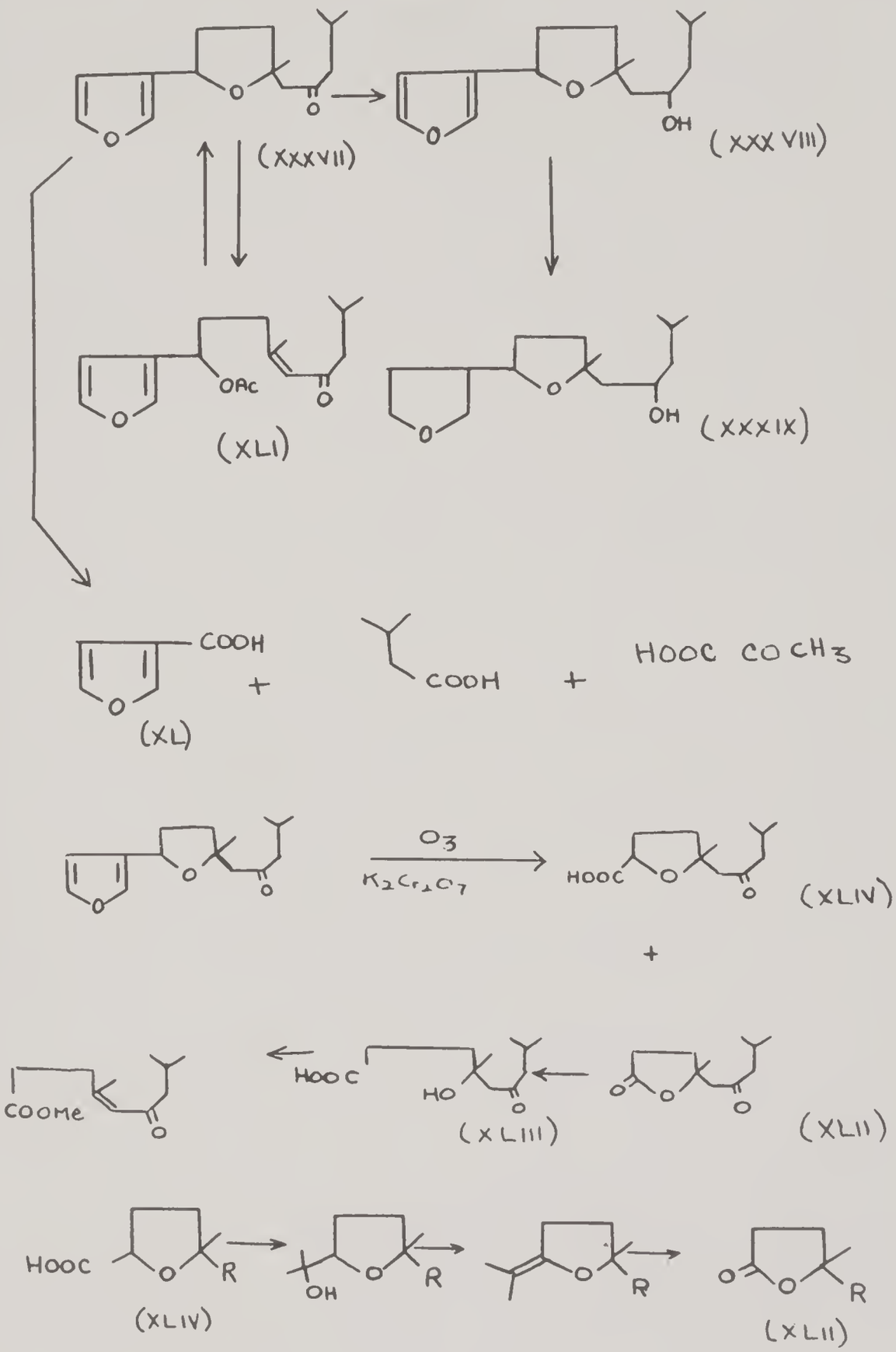
(XXXVI) (XXX) (XXXI)

(XXXV) (XXXII) (XXXIII) (XXXIV)

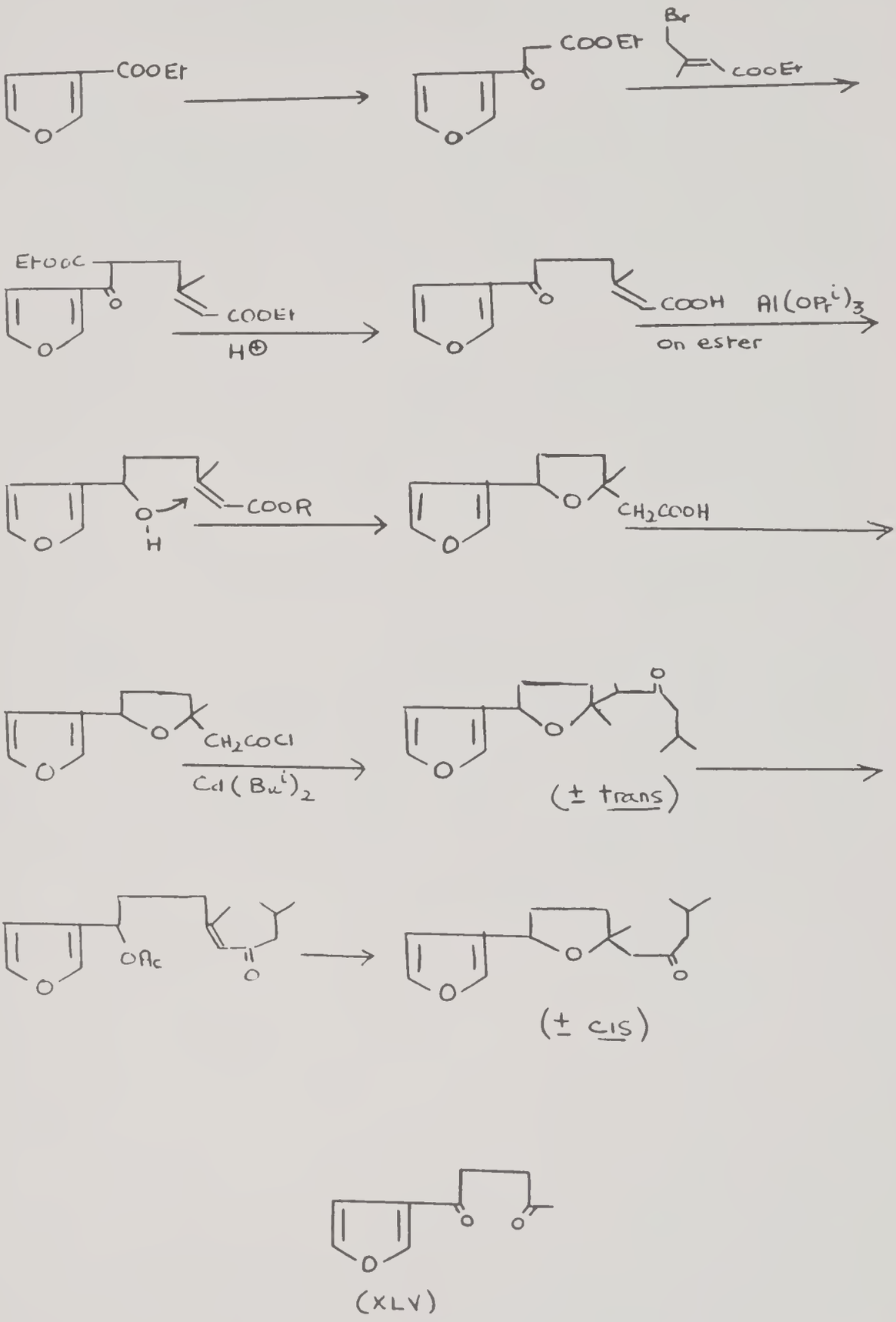
(XXXIII), and (XXXIV). Although these were the predicted products, evidence was also adduced for the presence of some of the *trans* isomer (XXXV) amongst the products, and therefore of the possible non-concerted nature of the process. The acids (XXXIII) and (XXXIV) were also obtained directly by the cyclisation of farnesenic acid, by the use of the same reagent at 35°, and indicated non-concertion. On the other hand, the monocyclic acids (XXX) and (XXXI) are unlikely to be intermediates in this transformation since they are themselves harder to cyclise than is the triene. It should be noted that the epimerisation of (XXXIII) to (XXXIV) represents a change from equatorial to axial and is an example of an unusual reversed stability because of overcrowding of the equatorial position by α-substituents (13).

Ngaione (XXXVII) occurs to the extent of about 80% in the essential oil obtained by steam distillation of the leaves of the New Zealand tree *Myoporum lactum* Forst. (14). It is a monoketone, contains two double bonds, and has no hydroxyl group. Reduction with sodium and alcohol gives a secondary alcohol, ngaiol (XXXVIII), hydrogenated to the saturated tetrahydrongaiol (XXXIX). By oxidation with ferricyanide, ngaione afforded 3-furoic acid (XL), *iso*-valeric acid, and pyruvic acid. Despite the absence of a hydroxyl group, acetylation with sodium acetate and acetic anhydride gives an acetate, *iso*ngaione acetate (XLI), reconverted to ngaione on hydrolysis. The former compound has a band in the ultra-violet ($\lambda_{max.}$ 238 mμ) not present in ngaione, indicative of conjugation. This reversible reaction, as shown, is a β-elimination and addition, but since the recovered product is racemic, the centre α to the furan ring must also be involved, as might be expected under the vigorous conditions used.

From the black-rotted portions of sweet potatoes (mainly due to *Ceratostomella fimbriata*) the enantiomer of ngaione, **ipomeamarone** (15), has been isolated, together with 3-furoic acid (XL). Amongst the degradative work carried out, that shown opposite is of particular interest. The lactone (XLII), ipomic lactone, on hydrolysis gave the corresponding hydroxy acid (XLIII) which on methylation and distillation gave methyl anhydroipomic acid ester. The structure of the lactone (XLII) has been confirmed by synthesis, and that of ipomeanic acid (XLIV) by conversion to this, as shown.


(XXXVII)
(XXXVIII)
OAc
(XLI)
OH
(XXXIX)
COOH
+
COOH
+
HOOC CO CH3
(XL)
O3
K2Cr2O7
HOOC
(XLIV)
+
COOMe
HOOC
HO
(XLIII)
(XLII)
HOOC
R
OH
R
R
R
(XLIV)
(XLII)

Finally, very recently (±)-ngaione [(±)-ipomeamarone] has been synthesised (15b) as shown opposite. A related compound, ipomeanine (XLV), has also been isolated from blackrotted potatoes, but is not terpenoid (16).

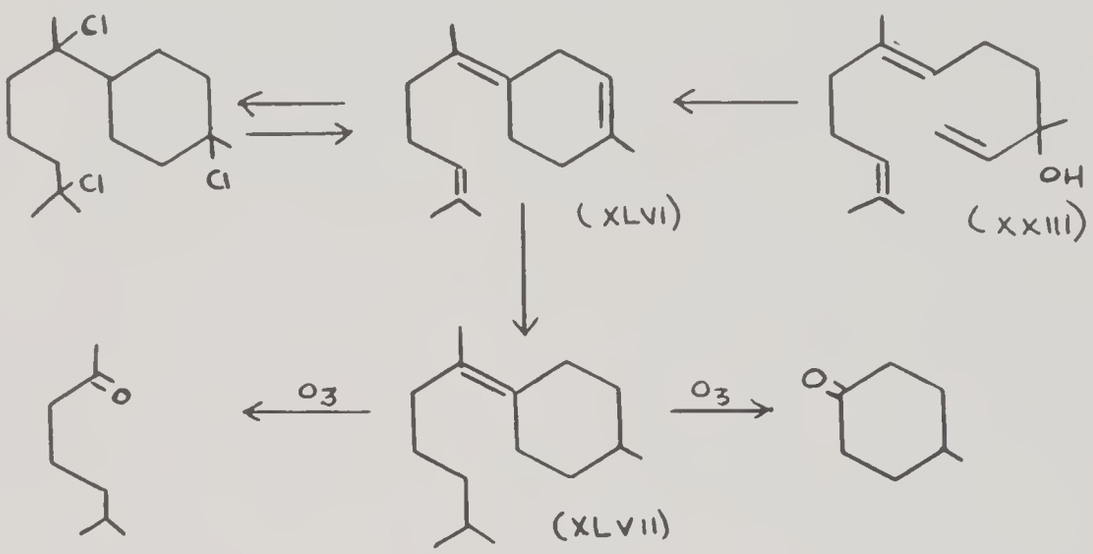

COOEt
COOEt
Br
COOEt
EtOOC
COOEt
H⊕
COOH
Al(OPr^i)3
on ester
COOR
CH2COOH
CH2COCl
Cd(Bu^i)2
(± trans)
OAc
(± cis)

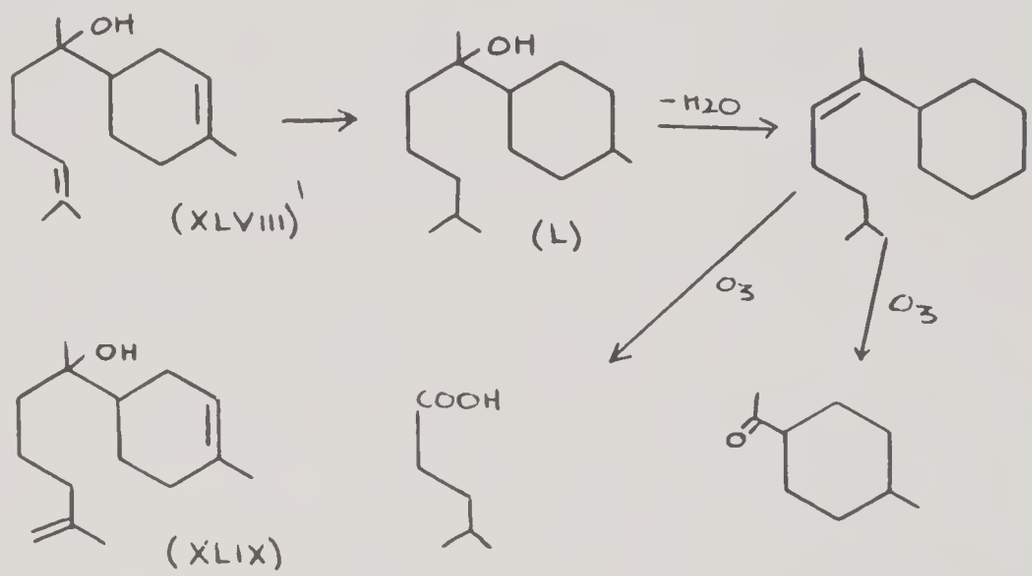
(XLV)

THE MONOCYCLIC SESQUITERPENOIDS

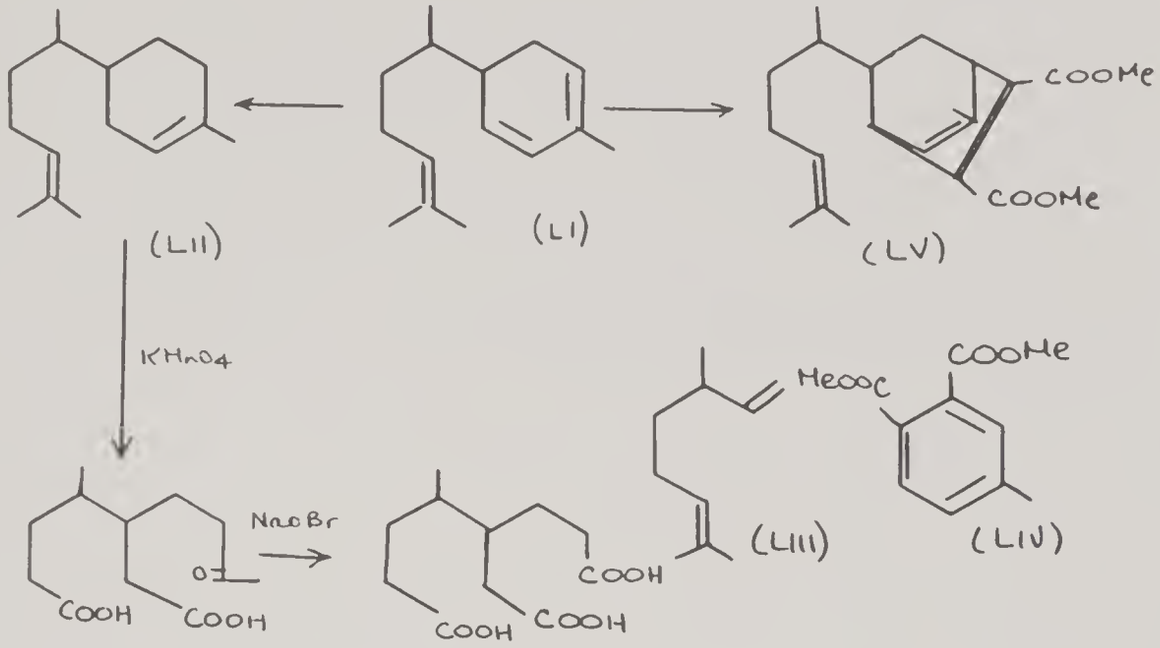
The Bisabolene Group

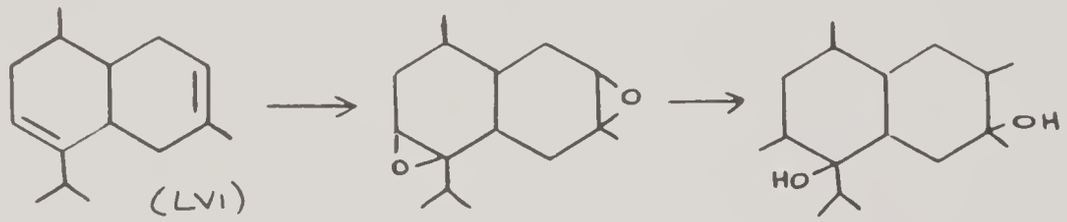
γ-Bisabolene (XLVI) is one of the most widely distributed of sesquiterpenoid hydrocarbons. It was first isolated in 1897, by Tucholka, from bisabol myrrh. It gives a characteristic trihydrochloride from which it can be regenerated with sodium acetate in acetic acid. It thus contains three double bonds and so, from its empirical formula, $C_{15}H_{24}$, must be monocyclic. Information as to its carbon skeleton was adduced from its production by the dehydration of nerolidol. Ozonolysis produced acetone, levulic acid, and succinic acid, and so gave an indication as to the location of the double bonds. Catalytic reduction in neutral solution gives (XLVII) and ozonolysis of this allowed, as shown, of the unequivocal placing of the fully substituted double bond. The formula has been confirmed by the synthesis of the trihydrochloride (17). The related alcohol, bisabolol (XLVIII), has been isolated (18) from camomile, its presence having also been previously suspected in French lavender oil. Its constitution is based on the reactions shown. Some of the isomeric (XLIX) has been supposed to be present since formaldehyde, as well as acetone, was obtained on ozonolysis, but such results should be treated with reserve. The alcohol (L) was synthesised. The formula (XLVIII) also has been proposed for the substance anymol derived from the wood of *Myoporum crassifolium* (19).

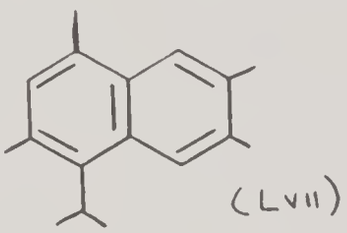

Cl
Cl
Cl
(XLVI)
OH
(XXIII)
O
O_3
O_3
O
(XLVII)


OH
(XLVIII)
OH
(L)
$-H_2O$
O_3
O_3
OH
(XLIX)
COOH
O

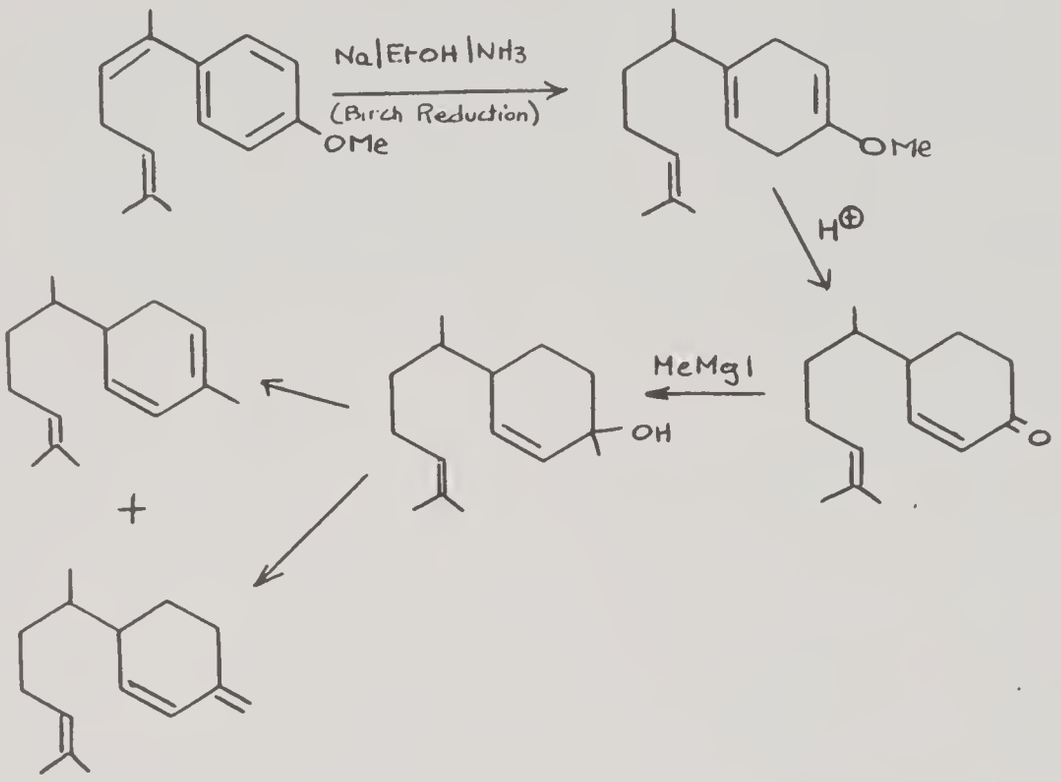
Zingiberene (LI) is the main constituent of ginger oil from *Zingiber officinale* Roscoe from which it was first isolated, in 1881, by Thresh. It is a conjugated diene as shown by its reduction, with sodium and alcohol, to dihydrozingiberene (LII) and by its absorption spectrum. Its carbon skeleton was indicated by the formation of cadalene on dehydrogenation. With dimethyl acetylenedicarboxylate the Diels-Alder adduct (LV) was formed which on pyrolysis gave (LIII) and (LIV), clearly establishing the entire structure. The position of the double bond in dihydrozingiberene was established by permanganate oxidation. With hydrogen chloride the hydrochloride of *iso*zingiberene (LVI) is formed. Recovery of the hydrocarbon gives *iso*zingiberene, which contains only two ethylenic linkages and is therefore bicyclic. Perbenzoic acid gives a diepoxide and with this, by the action of methyl magnesium iodide, a glycol is formed. Dehydration with formic acid and dehydrogenation with the quinone chloranil then gives (LVII). This establishes the position of the double bonds in *iso*zingiberene. The natural zingiberene may contain some isomeric dienes, and a mixture of hydrocarbons having properties similar to those of natural zingi-

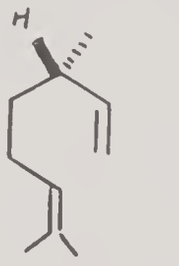

(LII)
(LI)
COOMe
COOMe
(LV)
KMnO4
NaOBr
COOH
COOH
COOH
COOH
MeOOC
COOMe
(LIII)
(LIV)


(LVI)
O
O
OH
HO

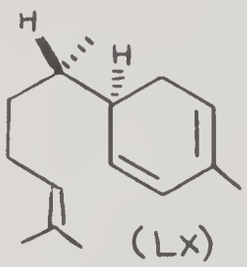

(LVII)

berene has been prepared (20) as shown opposite. The synthetic product likewise gave the Diels-Alder adduct with dimethylacetylene dicarboxylate. The (+) diene (LIII) from the pyrolysis of the adduct has been related to citronellal, the (+) form of the latter giving the (–) diene (21). The former compound therefore has the absolute configuration (LVIII). On the basis of rotatory powers the ring asymmetric centre of zingiberene has been shown (22) to be identical with that in (–)-α-phellandrene (LIX). (–)-Zingiberene must therefore have the absolute configuration (LX).

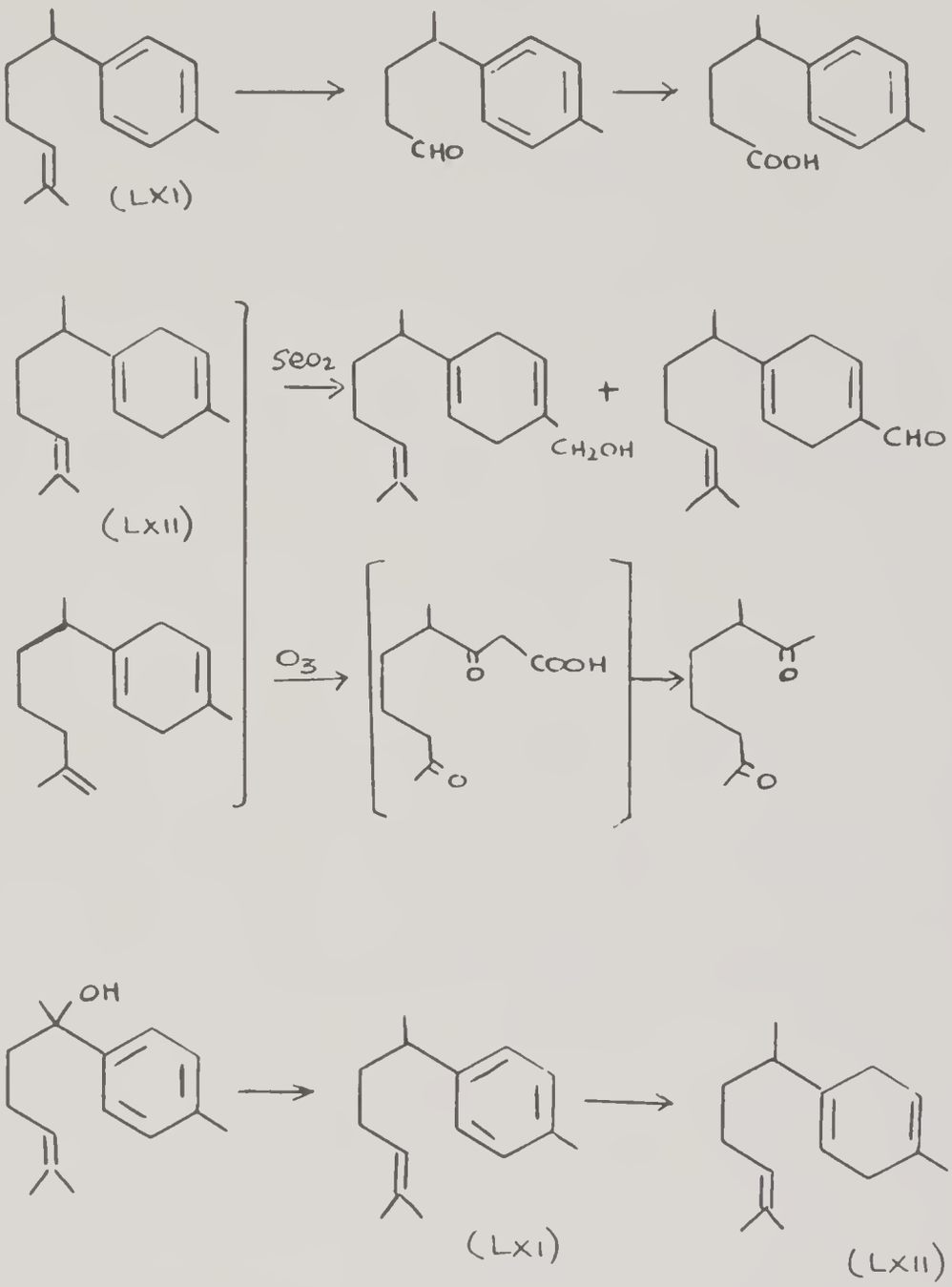



(LVIII)

(LIX)

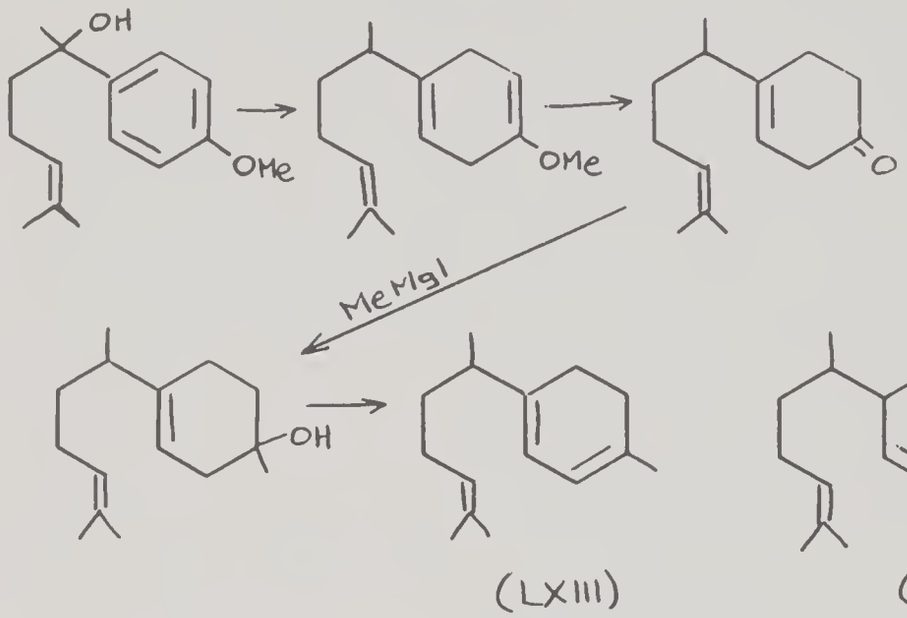

(LX)

α- and β-Curcumene, (LXI) and (LXII), have been isolated from the oil from the rhizomes of *Curcuma aromatica* Salisb. It is possible that some of the *iso*propenyl isomer may also be present. Their structures were deduced largely from the reactions shown. However, this evidence is not compelling in the case of the β isomer since bond migration may take place during allylic oxidation with selenium dioxide. γ-Curcumene, for which the structures

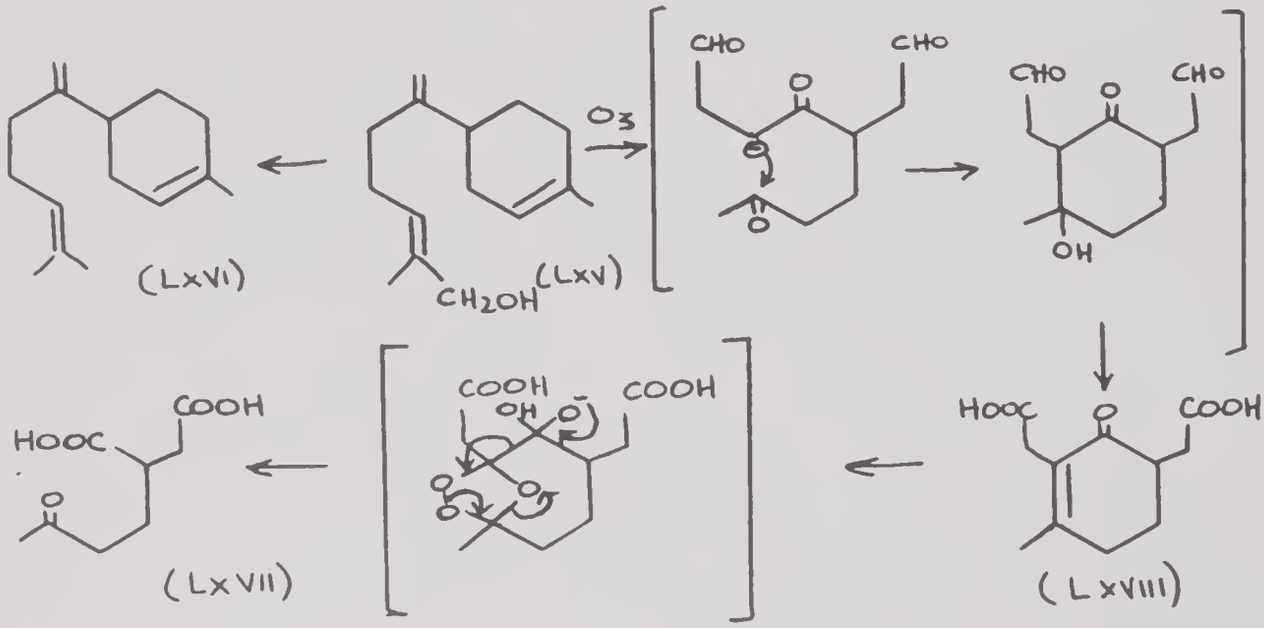

CHO
COOH
(LXI)
SeO2
CH2OH
CHO
(LXII)
O3
COOH
OH
(LXI)
(LXII)

(LXIII) or (LXIV) are possible, has been isolated from *Libocedrus bidwillii*. Syntheses of hydrocarbons corresponding in properties to the curcumenes have been reported by Birch and Mukherji using the valuable metal–liquid ammonia reduction (23) both for hydrogenolysis of a benzylic alcohol and for the reduction of the benzene ring. If during the Grignard reaction the double bond moves into conjugation with the ketone prior to reaction, then (LXIV) might be amongst the expected products.

Lanceol (LXV) is a primary alcohol isolated from *Santalum lanceolatum*. Its structure has been shown (24) by two complementary methods. Reduction with sodium in liquid ammonia-ethanol hydrogenolysed the alcohol (which is therefore allylic) and gave an isomer of β-bisabolene (LXVI). Ozonolysis of lanceol gave formaldehyde, hydroxyacetone, and a keto dicarboxylic acid. This was an α-β-unsaturated ketone and contained no other ethylenic linkage. On further ozonolysis the acid (LXVII) was obtained. The intermediate ketodicarboxylic acid is not a primary product of the ozonolysis, but is formed by an aldol condensation from the ketonic precursor. The reaction has been formulated as shown and the acid (LXVIII) synthesised. The formation of (LXVII) involves either the loss of carbon dioxide from a β-keto acid and the cleavage of an α-diketone, possibly by peroxide present during the ozonolysis, or the direct hydrolytic cleavage of the ozonide (59).



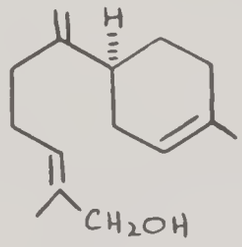
(LXIII) (LXIV)



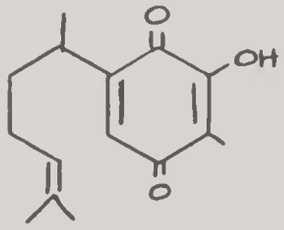
(LXVII) (LXVIII)

On the basis of rotatory powers Mills (22) has related (–)-lanceol to (–)-limonene and it thus has the absolute configuration (LXIX).

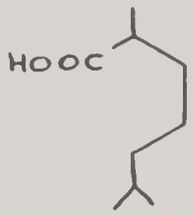
Perezone (LXX) is the only sesquiterpenoid quinone so far discovered. It was first isolated by Weld, in 1855, from the roots of *Trixis pipitzahuac* Schaffner. It is readily reduced giving a *leuco* compound, itself easily oxidised back to perezone in air. The hydroxyl group is acidic since it forms metallic salts and these facts are indicative of a monohydroxyquinone. The presence of unsaturation in a side-chain was shown by the formation of an unstable dibromide. Oxidation with alkaline hydrogen peroxide (24) gave a nonenoic acid (with disruption of the ring) which was hydrogenated to 2 : 6-dimethylheptanoic acid (LXXI). These experiments showed the presence of two side-chains, one a methyl group and the other a 1 : 5-dimethylhexenyl group attached to the quinone nucleus. By reaction with aniline perezone gives a monoanilino (LXXII) derivative hydrolysed by sulphuric acid to hydroxyperezone (LXXIII). The former is formed by addition of aniline and abstraction of two hydrogens during the reaction; hydrogenation of (LXXIII) gives (LXXIV). Reduction to (LXXVI) and formation of the tetramethyl ether followed by zinc distillation and oxidation with chromic acid then gave terephthalic acid. The C_1 and C_8 side-chains are thus attached *para* to each other. The position of the ethylenic linkage in the side-chain was found by ozonolysis of *leuco*perezone triacetate (LXXV) to give acetone. The acid (LXXI) is laevorotatory and the same acid has been prepared, by degradation, from (+)-citronellal. It follows (21) that (–)-perezone has the absolute configuration (LXXVI). (±)-Dihydroperezone has been synthesised by Yamaguchi (25). Amongst other compounds of this group, which have been ascribed formulae, may be mentioned (27) *ar*-turmerone (LXXVII), turmerone (LXXVIII), and the atlantones (LXXIX).



(LXIX)

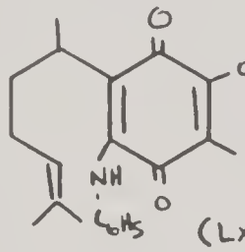


(LXX)

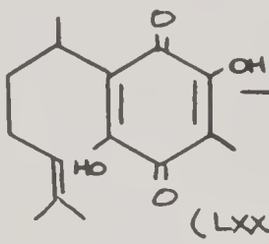


(LXXI)

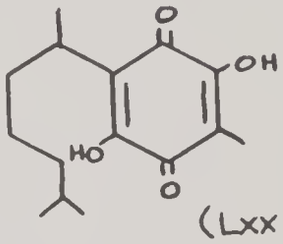
(LXX) →



(LXXII)

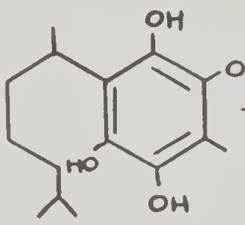


(LXXIII)

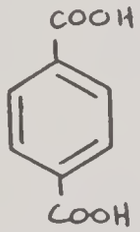


(LXXIV)

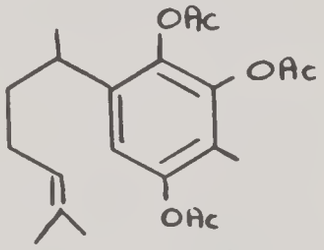
→



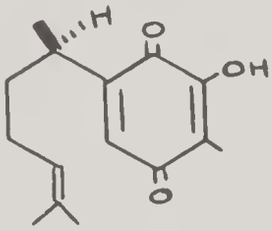
(LXXVI)



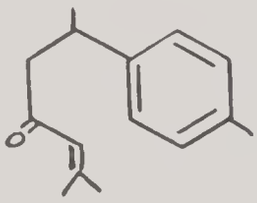
(Terephthalic acid)



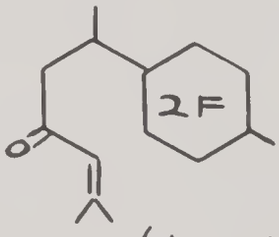
(LXXV)



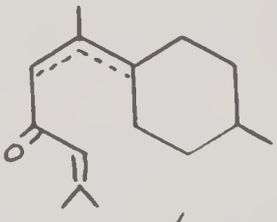
(LXXVI)



(LXXVII)



(LXXVIII)



(LXXIX)

BICYCLIC SESQUITERPENOIDS

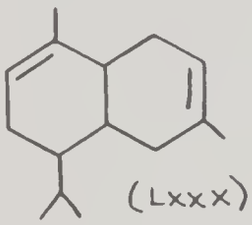
The Cadalene Group and Related Compounds

α-Cadinene (LXXX) is very widely distributed in nature and was first isolated from oil of cubebs in 1840. It contains two ethylenic linkages and since, on dehydrogenation, it gives cadelene as already mentioned, the structural problem is that of assigning the position of the double bonds. α-Cadinene with perbenzoic acid gives a diepoxide, and this, with methyl magnesium iodide, affords the diol (LXXXI). Dehydrogenation then gave (LXXXII) (26). However, although this is unambiguous as far as the diene giving the diepoxide, it is improbable either that the cadinene in nature is homogeneous or that that recovered from its characteristic dihydrochloride should be (28). From the oils of citronella, sweet flag, and ylang-yland a number of isomeric cadinenes have been isolated (29) such as ε-cadinene (LXXXIII). All give cadinene dihydrochloride. α-Cadinene has not been synthesised. Amongst other hydrocarbons in this series are sesquibenihene (LXXXIV) and calamenene (LXXXV), the latter having been synthesised (30), but they do not require special comment. Copaene is a related tricyclic substance giving cadinene dihydrochloride with hydrogen chloride; it is believed to contain a *cyclo*propane ring. The structure (LXXXVI) (31) has been generally accepted, but seems imporbable since the formation of the dihydrochloride would involve non-Markownikoff opening of the *cyclo*propane ring. The objection would not apply to the structures (LXXXVII) and (LXXXVIII) both of which could be adequate vehicles for the presently available evidence.

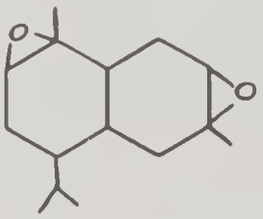
A number of alcohols in this class are known to which structures have been assigned (32). Some of these, such as the isomeric cadinols, have not been obtained pure. Ledol was formerly assigned to this class, but it has recently been suggested that it is a perhydroazulene derivative; this has not been conclusively established.

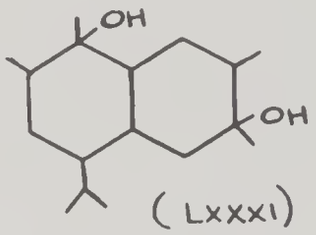
The Eudalene Group and Related Compounds

The hydrocarbon **selinene** was first isolated in 1897 from the fruit of *Apium graveolens*. On dehydrogenation it gives eudalene

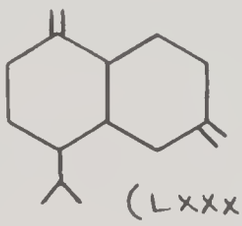


(LXXX)

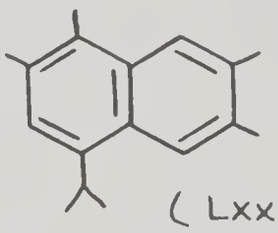




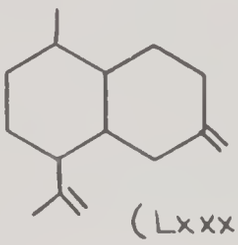
(LXXXI)



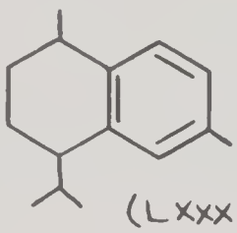
(LXXXIII)



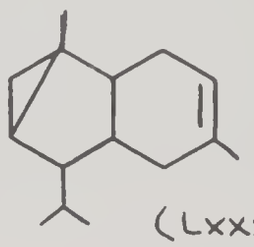
(LXXXII)



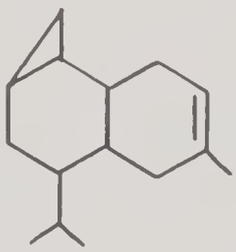
(LXXXIV)



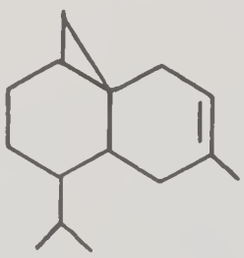
(LXXXV)



(LXXXVI)



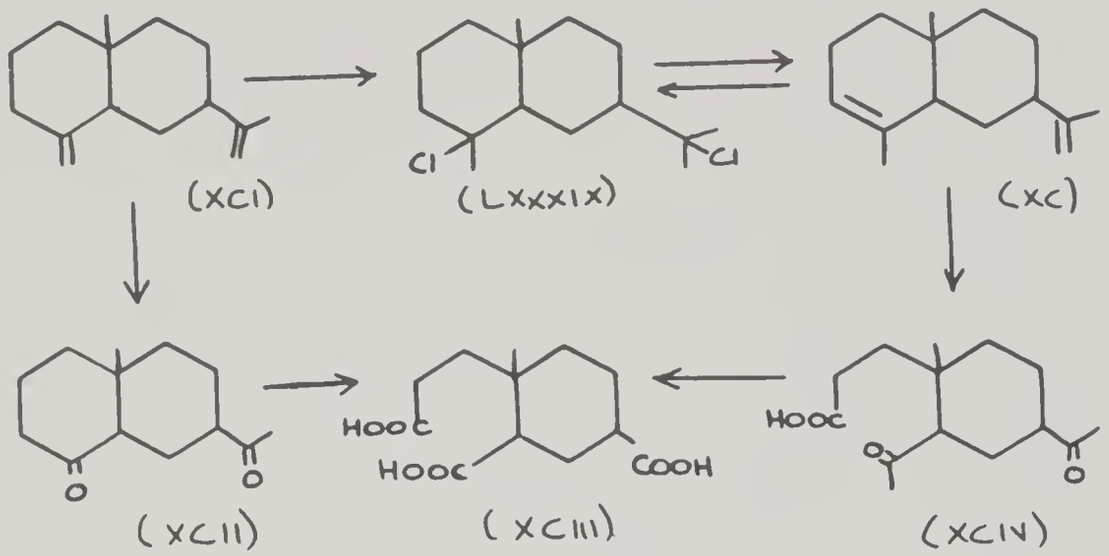
(LXXXVII)

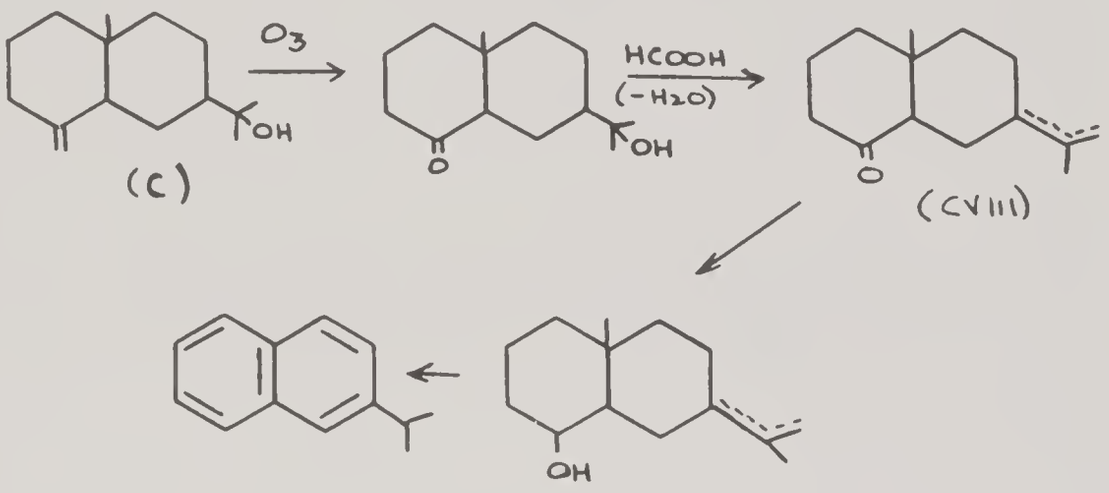


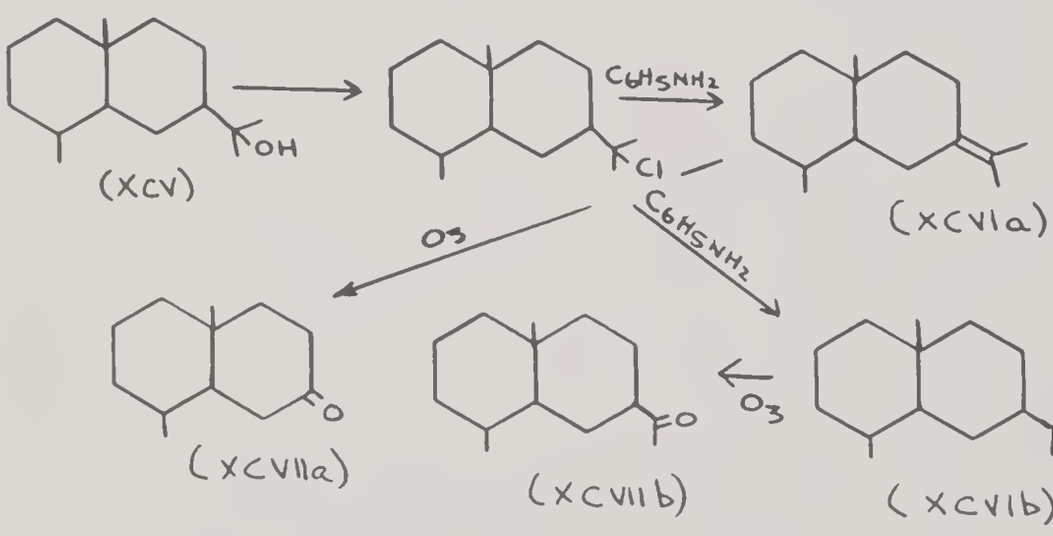
(LXXX VIII)

and, with hydrogen chloride, a characteristic dihydrochloride (LXXXIX) is obtained. On regeneration of the hydrocarbon the original compound is not recovered. The difference between the latter compound (α-selinene (XC)) and the natural material (β-selinene (XCI)) was established by examination of their ozonolysis products. β-Selinene gave a diketone (XCII) oxidised to (XCIII), a tricarboxylic acid. α-Selinene, on the other hand, gave a diketonic acid (XCIV) which was further oxidised (hypobromite) to the same acid (XCIII). This work, together with the relationship of selinene dihydrochloride to eudesmol mentioned below, establishes unambiguously the structures of the selinenes (32).

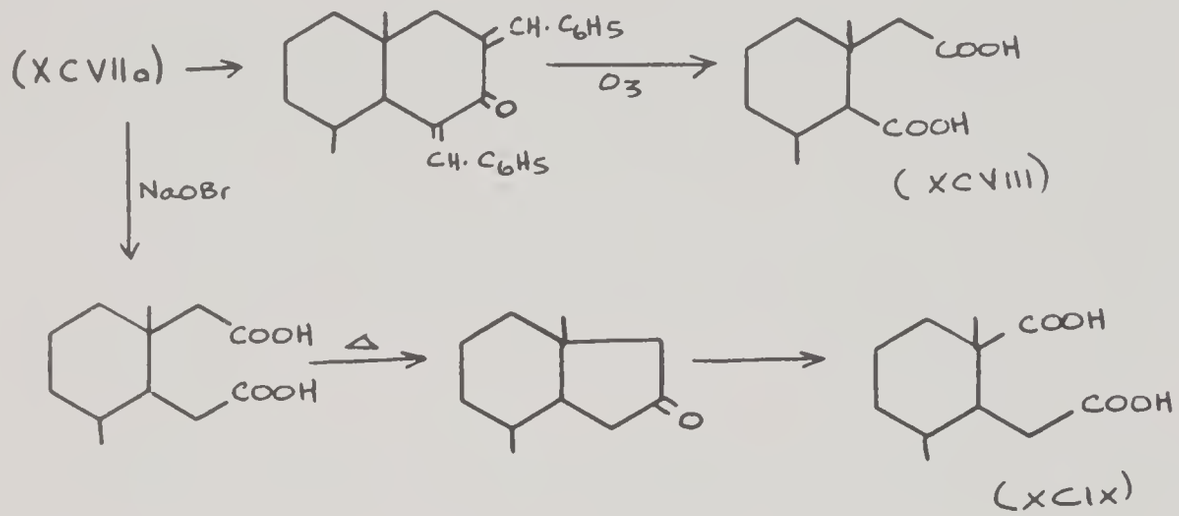
Eudesmol (C) is a crystalline alcohol obtained from the essential oil of *Eucalyptus piperita.* With hydrogen chloride it gives selinene dihydrochloride (LXXXIX), whilst dehydrogenation gives eudalene. The position of the one ethylenic linkage was demonstrated by the sequence of reactions shown. Catalytic hydrogenation of eudesmol gives dihydroeudesmol (XCV). This was converted as shown to dihydroeudesmene (XCVIa and XCVIb). Ozonolysis then gave formaldehyde, acetone, and (XCVIIa) and (XCVIIb), thus establishing the position of the hydroxyl group. The remaining feature requiring elucidation, structurally, was the position of the angular methyl group allocated on the basis of the isoprene rule, but needing further confirmation in view of the anomaly presented by ere-

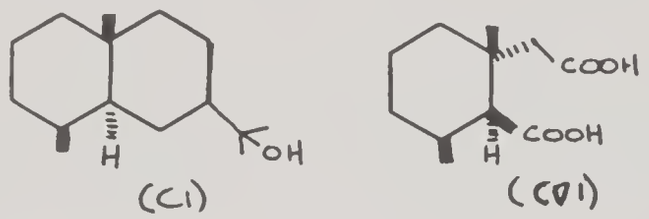

(XCI)
Cl
Cl
(LXXXIX)
(XC)
O
O
(XCII)
HOOC
HOOC
COOH
(XCIII)
HOOC
O
O
(XCIV)

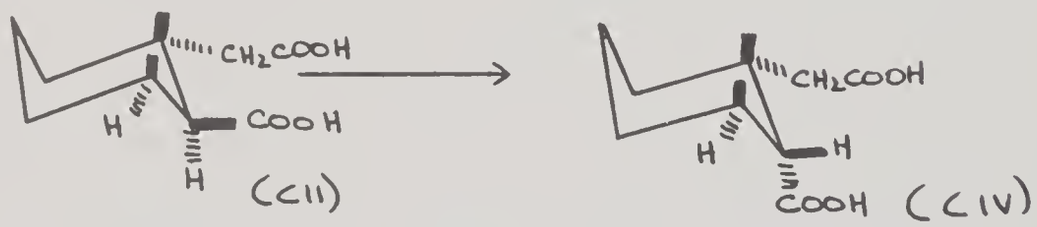

O_3
OH
(C)
HCOOH
(-H2O)
OH
O
(CVIII)
OH

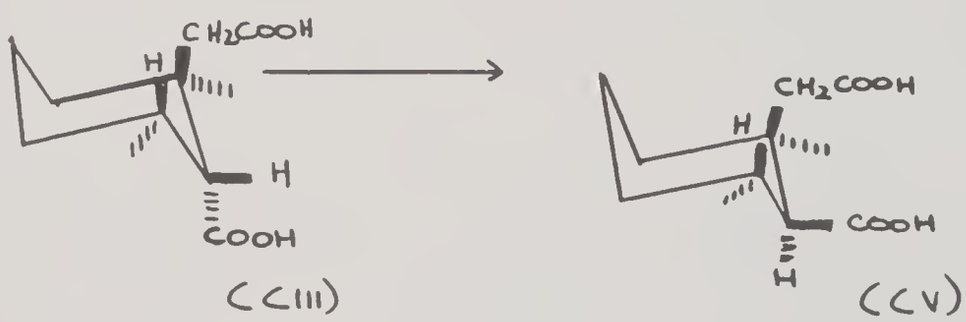

OH
(XCV)
C6H5NH2
Cl
(XCVIa)
O3
C6H5NH2
O
(XCVIIa)
O
(XCVIIb)
O3
(XCVIb)

mophilone. Conversion of (XCVIIa) into the *bis*benzylidene compound and ozonolysis gave a dicarboxylic acid (XCVIII). This could have had the alternative structure (XCIX), but on treatment with concentrated hydrochloric acid it was epimerised to an isomeric acid. One of the carboxyl groups must, therefore, be attached to an asymmetric carbon atom bearing a hydrogen atom. The acid (XCIX) was prepared by the route shown. It has been proposed that the epimerisation of the acid (XCVIII) indicates that the original fusion of the rings was *cis*, the acid then isomerising to the *trans*. Barton has shown, however, that assuming a *trans* fusion and hydrogenation from the less hindered side of the molecule, dihydroeudesmol would be represented as (CI). (XCVIII) now (CVI) will then be represented as having either conformation (CII) or (CIII). In either case isomerisation of the secondary carboxyl would be expected, giving the more stable conformations (CIV) or (CV) because of the inversion of stability of axial relative to equatorial substituents in heavily α-substituted rings (13). The same conclusion was reached on the basis of molecular rotations (34). The relative configuration of the *iso*propyl group was shown by equilibration (with alcoholic potash at 210°) of the ketone (XCVIIb). It was not epimerised and is thus in the stable, equatorial, configuration—that is, on the same side of the molecule as the angular methyl group. The relation of eu-


(XCVIIa)
CH·C6H5
O
CH·C6H5
O3
COOH
COOH
(XCVIII)
NaOBr
COOH
COOH
Δ
O
COOH
COOH
(XCIX)

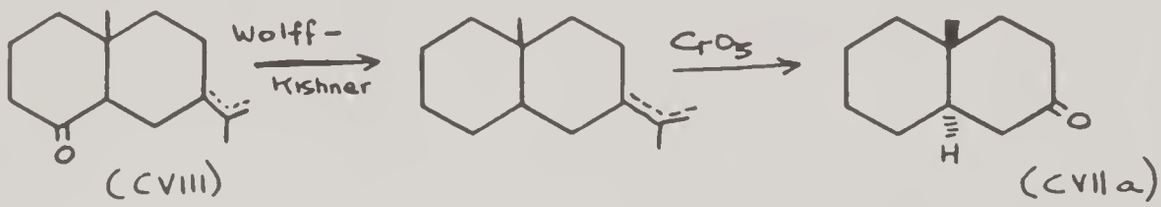

H
OH
(CI)
COOH
COOH
H
(CII)


CH2COOH
H
COOH
H
(CII)
CH2COOH
H
H
COOH
(CIV)


CH2COOH
H
H
COOH
(CIII)
CH2COOH
H
COOH
H
(CV)

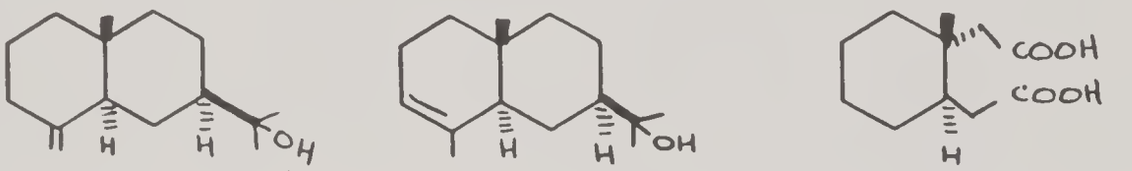
desmol to the steroids, so giving its absolute configuration, was accomplished by conversion to the ketone (CVIIa) and dicarboxylic acid (CVIIb), which were the enantiomorphs of derivatives obtained from intermediates in the Woodward total synthesis of steroids. The absolute configuration of eudesmol is therefore as represented in (CIX) (35). As is the case with many terpenoids, the natural product is contaminated with isomers and the formulation (CIX) is that of β-eudesmol. α-Eudesmol (CX) is also believed to be present.

Elemol, a crystalline doubly unsaturated tertiary alcohol, was first isolated from the Manila oil of elemi. It was subsequently investigated by Ruzicka and his collaborators (33). On the basis of dehydrogenation to eudalene and vetivazulene and of ozonolytic degradation they proposed the formula (CXI), suggesting the possible presence of a small amount of the isomer (CXII). The compound has recently been reinvestigated by Sorm and his colleagues (37). If (CXI) represented elemol, then elemane, the saturated hydrocarbon obtained by dehydration and reduction, would be (CXIII). This compound was synthesised, as shown, and was found not to be identical with elemane. Careful inspection of the infra-red spectrum of elemol then revealed that there were *two* terminal methylene groups, one $CR_2{=}{=}CH_2$ and one $CHR{=}{=}CH_2$ as indicated by bands at 891, 911, 1006, and 1641 cm^{-1}. Further, quantitative ozonolysis revealed that two molecules of formaldehyde were formed. This being so, the available evidence indicated that the correct

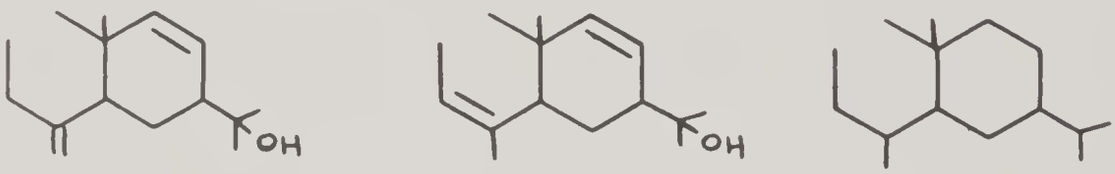


(CVIII) (CVIIa)

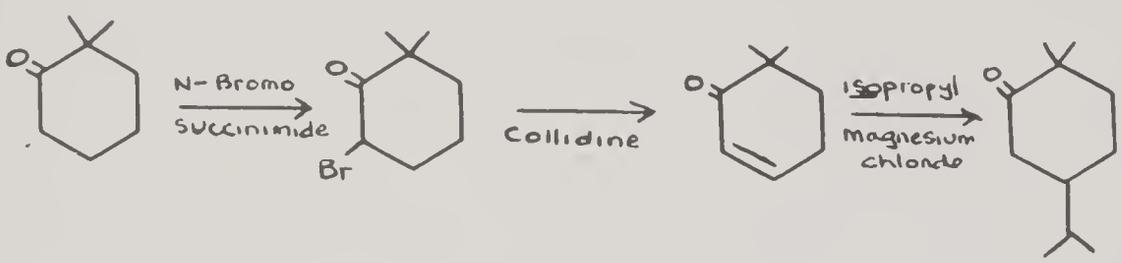
+

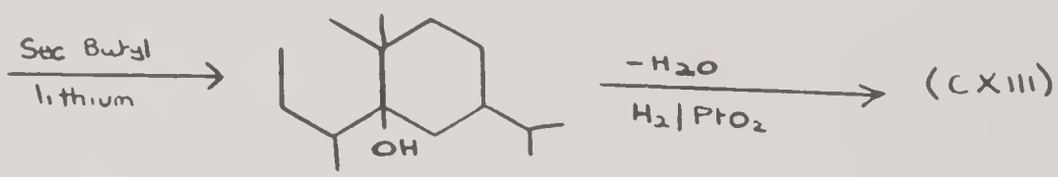


(CIX) (CX) (CVIIb)



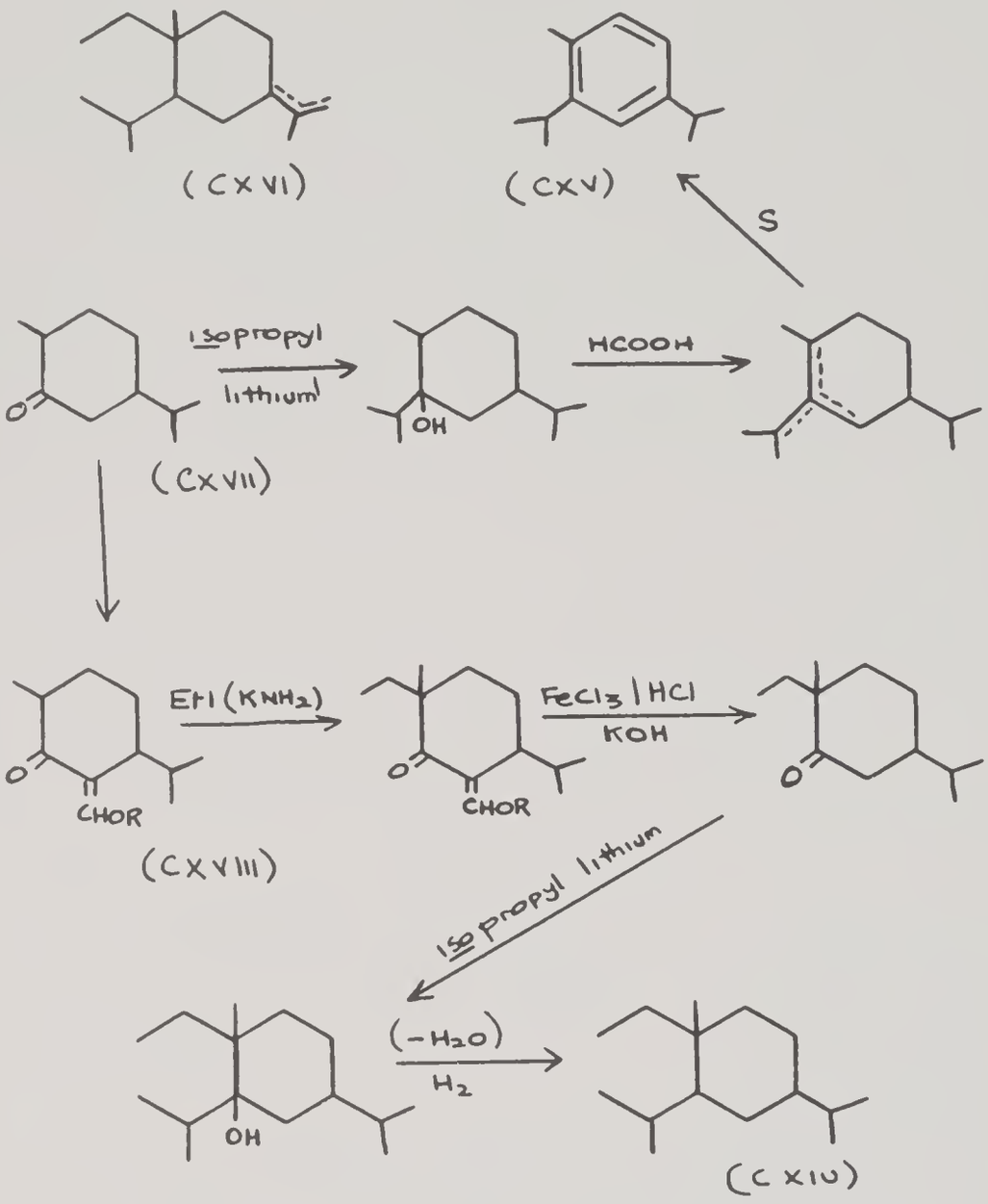
(CXI) (CXII) (CXIII)





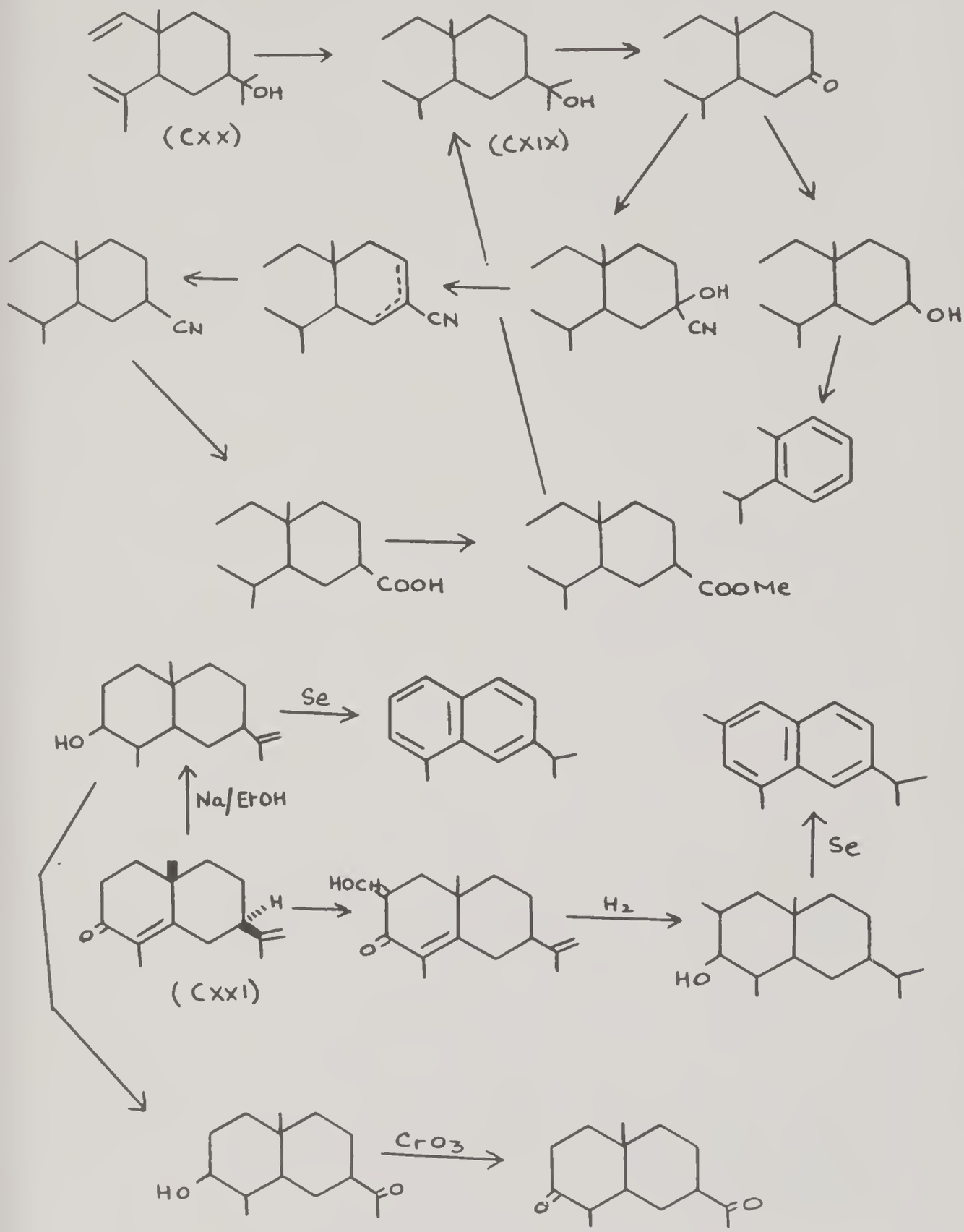
(CXIII)

structure for elemane must be (CXIV). It then followed that a compound previously obtained by sulphur dehydrogenation of tetrahydroelemene (CXVI) must be (CXV); this conclusion was verified by synthesis, as indicated, from carvomenthone (CXVII). This work, as far as the skeletal framework was concerned, was completed by the synthesis of elemene from carvomenthone. This was first alkylated, after blocking the methylene group α to the ketone by formation of the hydroxymethylene (CXVIII, R = H) derivative (with ethyl formate) and conversion to the butyl ether (CXVIII, R = Bu). After alkylation the blocking group was converted to the ferric complex with ferric chloride, hydrolysed to the formyl derivative, and cleaved (β-dicarbonyl compound) with alkali. The final proof of the


(CXVI)
(CXV)
S
isopropyl
lithium
OH
HCOOH
(CXVII)
Et I (KNH2)
CHOR
FeCl3 | HCl
KOH
(CXVIII)
isopropyl lithium
(-H2O)
H2
OH
(CXIX)

structure of elemol (CXX) followed from the series of reactions starting with tetrahydroelemol (CXIX) outlined opposite. The structure (CXX), whilst built from three isoprene units, is not derived from a farnesyl chain and it has been suggested (38) that it is formed from a eudesmane-type precursor by ring opening.

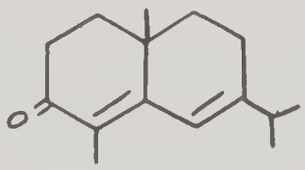
α-Cyperone (CXXI) was isolated from the tubers of *Cyperus rotundus* and its structure elucidated by the work of Simonsen and his collaborators (39), essentially as shown. Some of its reactions have been further investigated by McQuillin (40) and its absolute configuration has been established as being as shown in (CXXI) (34,40). The latter author has synthesised α-cyperone. Related


OH
(CXX)
OH
(CXIX)
O
CN
CN
OH
CN
OH
COOH
COOMe
HO
Se
Na/EtOH
H
HOCH
O
O
(CXXI)
H₂
Se
HO
HO
CrO3
O
O

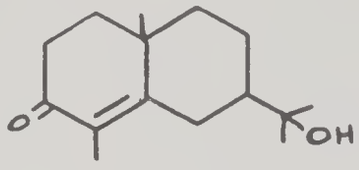
compounds are β-cyperone (CXXII) and carissone (CXXIII). The latter was isolated by Mohr, Schindler, and Reichstein (41) from the roots of *Carissa lanceolata.* Dehydration with phosphorus oxychloride in pyridine (42) and conversion into the 2:4-dinitrophenylhydrazone gave the derivative of β-cyperone. Dehydration of the 2:4-dinitrophenylhydrazone of the original compound gave that of α-cyperone. During the formation of the derivative, therefore, the ethylenic linkage introduced by dehydration migrates into conjugation.

Santonin (CXXV) and a number of related compounds occur in various species of *Artemisia* which are widely distributed in nature, particularly in parts of Russia and India and in Iran and Turkestan. Santonin is itself widely used as an anthelmintic.

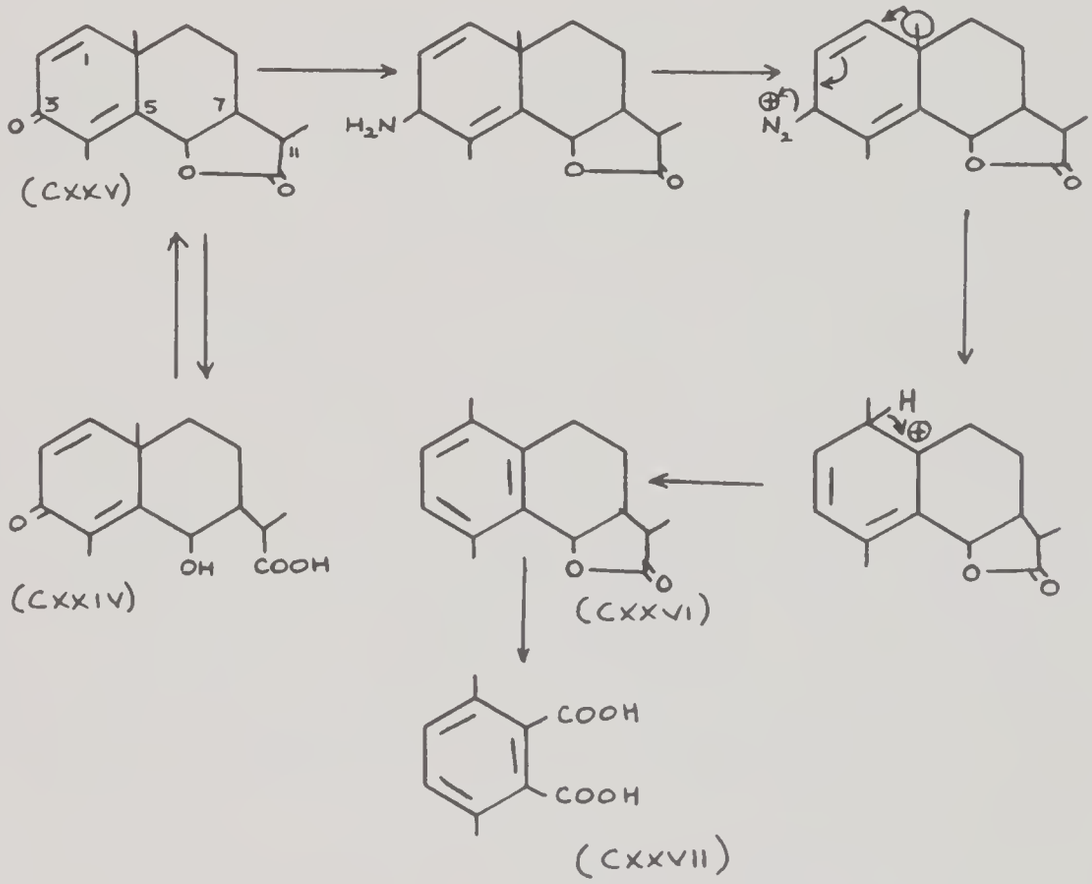
Santonin is a ketonic lactone containing two double bonds; on solution in alkali it gives salts of santoninic acid (CXXIV) from which it can be recovered unchanged on acidification. Much of the early work was carried out by Cannizzaro (43) and his coworkers. Amongst other important findings they showed that on distillation with zinc dust 1:4-dimethylnaphthalene, propylene, and some 1:4-dimethylnaphthol were obtained. Also, when santonin oxime was reduced by zinc dust and alcoholic sulphuric acid it gave the corresponding amine, santoninamine, which by treatment with nitrous acid gave a lactone, hyposantonin. This compound (CXXVI), together with a stereoisomer, was also obtained, surprisingly, by the reduction of the oxime, its acetate, or of the phenylhydrazone with sodium amalgam. It will be noted that in the formation of hyposantonin there has been the migration of the angular methyl group from the angular position in the attainment of aromaticity. It was this single feature, occurring in a number of santonin transformations, that caused the considerable difficulties involved in the elucidation of the santonin structure. Both hyposantonin and the isomer give 3:6-dimethylphthalic acid (CXXVII) on oxidation with permanganate, and since the lactonic function in (CXXVI) is the same as in santonin, this therefore indicated that at least one methyl group, and the ketonic function, were in the ring unattached to the lactone. Hyposantonin and its isomer with alcoholic hydrochloric acid are



(CXXII)



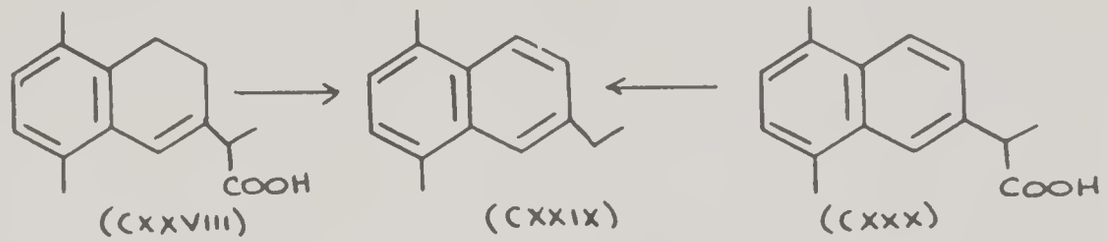
(CXXIII)



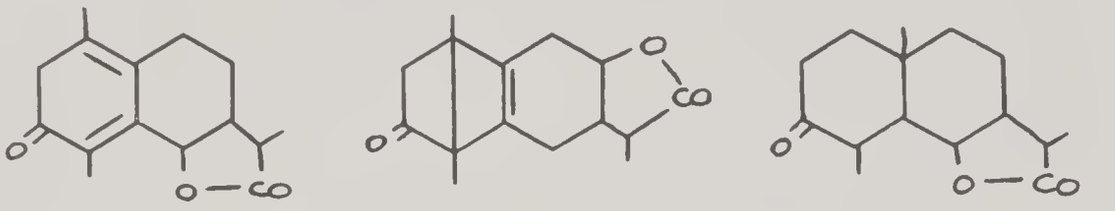
isomerised to two acids, dihydrosantinic acid (CXXVIII) and *iso*-dihydrosantinic acid. On heating with barium hydroxide, (CXXVIII) is converted into the hydrocarbon (CXXIX). When hyposantonin or dihydrosantinic acid was oxidised with iodine in acetic acid it was converted to the naphthalenic acid, santinic acid (CXXX). This, too, with barium hydroxide gave (CXXIX).

These reactions taken together established the position of the side-chain. They also suggested that the two double bonds in santonin, as well as the ketonic function, were in the same ring; however, all formulae proposed containing two ethylenic linkages were merely tautomerides of phenols (e.g., CXXXI), whereas santonin shows no phenolic properties. To avoid this it was suggested that santonin contained three rings (as CXXXII), but this hypothesis was soon disproved by catalytic hydrogenation to a (separable) mixture of two stereoisomeric tetrahydrosantonins (CXXXIII). Another reaction exemplifying the facile conversion of santonin into aromatic compounds was noted when it was observed that on treatment with fuming hydrochloric acid in the cold desmotroposantonin (CXXXIV) was obtained. A number of stereoisomers of this compound are now known.

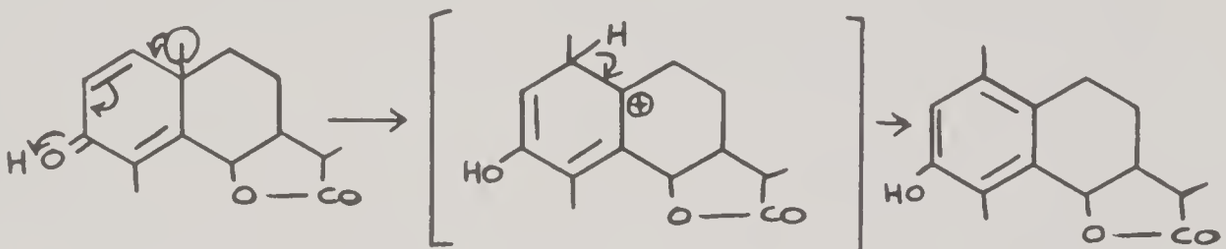
The correct formula for santonin was proposed in 1929 by Clemo, Haworth, and Walton (44), when it was suggested that although santonin was a sesquiterpenoid previous formulae had not been theoretically constructable from isoprene units. They confirmed their theory by synthesis of santanous acid (CXXXV), a substance obtained by the reduction of santonin with red phosphorus and hydriodic acid. The position of the attachment of the ether oxygen of the lactone ring, not indicated by this work, was established by the synthesis of desmotroposantonin (CXXXIV). Evidence was then required as to the position of the eliminated angular methyl group. This was forthcoming by a study of the permanganate oxidation products of santonin as shown. The acid (CXXXVI) was synthesised.



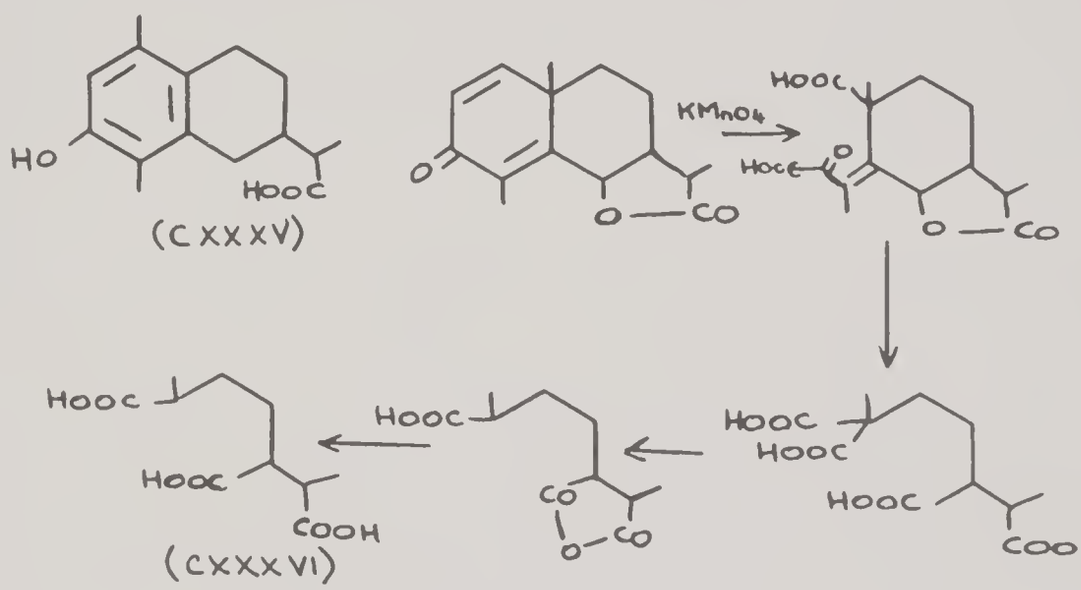
(CXXVIII) (CXXIX) (CXXX)



(CXXXI) (CXXXII) (CXXXIII)



(CXXXIV)

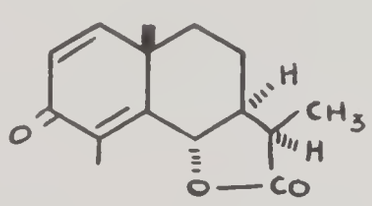


(CXXXV) (CXXXVI)

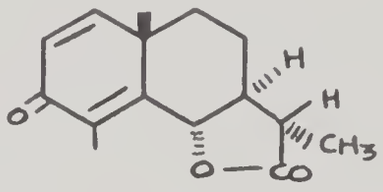
The stereochemistry of santonin has been the subject of much discussion. β-Santonin, also naturally occurring, is known to be the C_{11} epimer of santonin, but as yet this centre remains the only one the configuration of which has not been established with rigidity (45). The stereoformulae for santonin and β-santonin, (CXXXVII) and (CXXXVIII) or *vice versa,* represent the absolute configuration (60). The structures assigned to santonin and β-santonin have been confirmed by a group of Japanese workers by excellent syntheses (46), one of which is outlined opposite. Michael addition of ethyl methylmalonate to the dienone (CXXXIX) followed by enol-acetylation gave (CXL). Oxidation with peracetic acid with enol hydrolysis gave the lactone (CXLI), possibly by the stages shown. Bromination and dehydrobromination afforded the dienone (CXLII), which was then resolved through its brucine salt. After decarboxylation (–)-santonin, identical with natural santonin, was obtained. During the course of these experiments four other racemic santonin isomerides were prepared in which the rings were *cis*-fused.

The elucidation of the structure of santonin did not remove all barriers to the interpretation of the more exotic facets of santonin chemistry. Two examples of such studies may be commented on very briefly here.

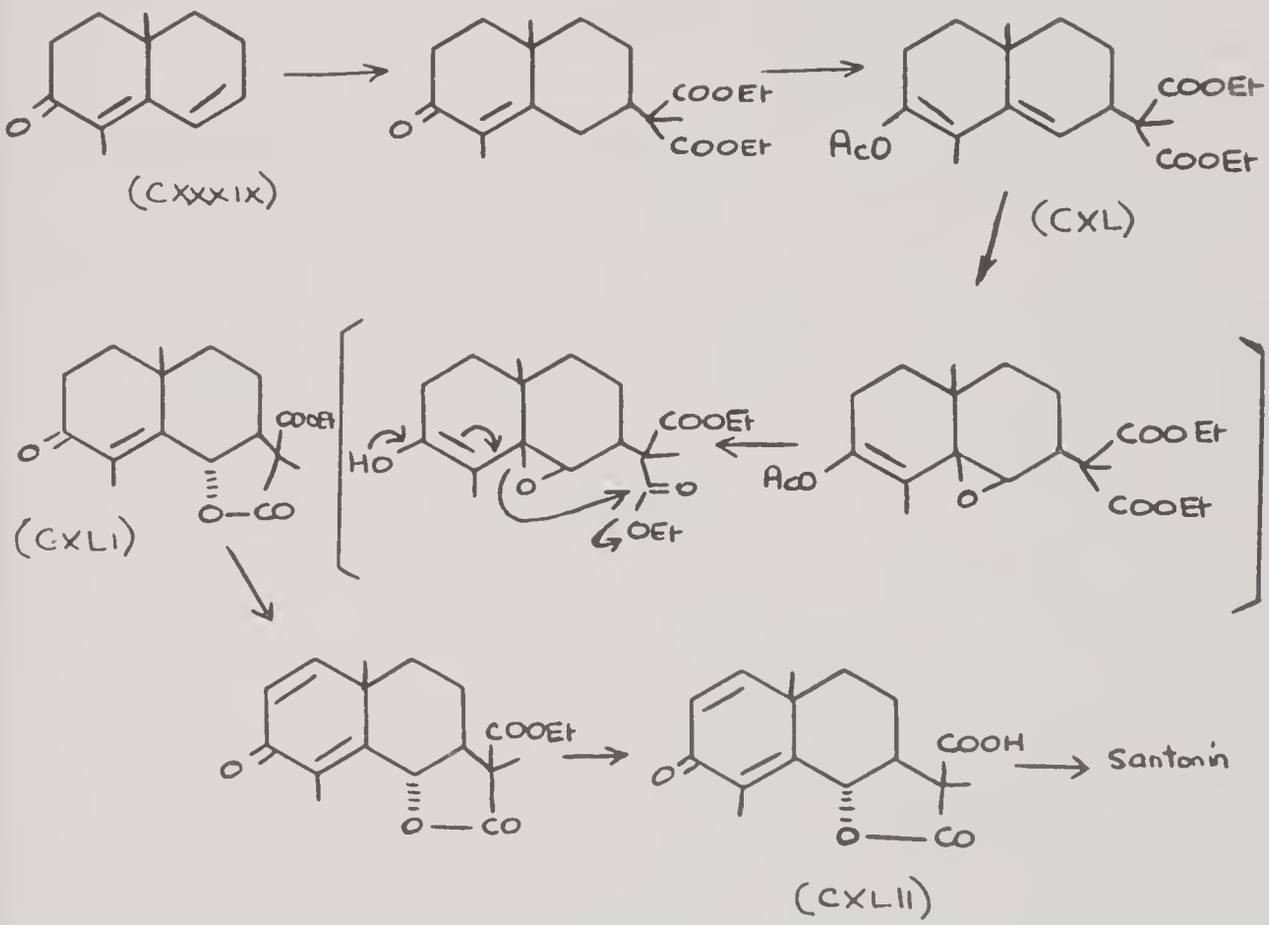
On prolonged treatment with alkali, such as hot saturated barium hydroxide solution, santonin is converted into santonic acid. This substance contains two ketonic functions, as shown by formation of *bis* oximes, etc., but does not contain a double bond. This transformation has been known since 1873, but interpretation of the large



(CXXXVII)

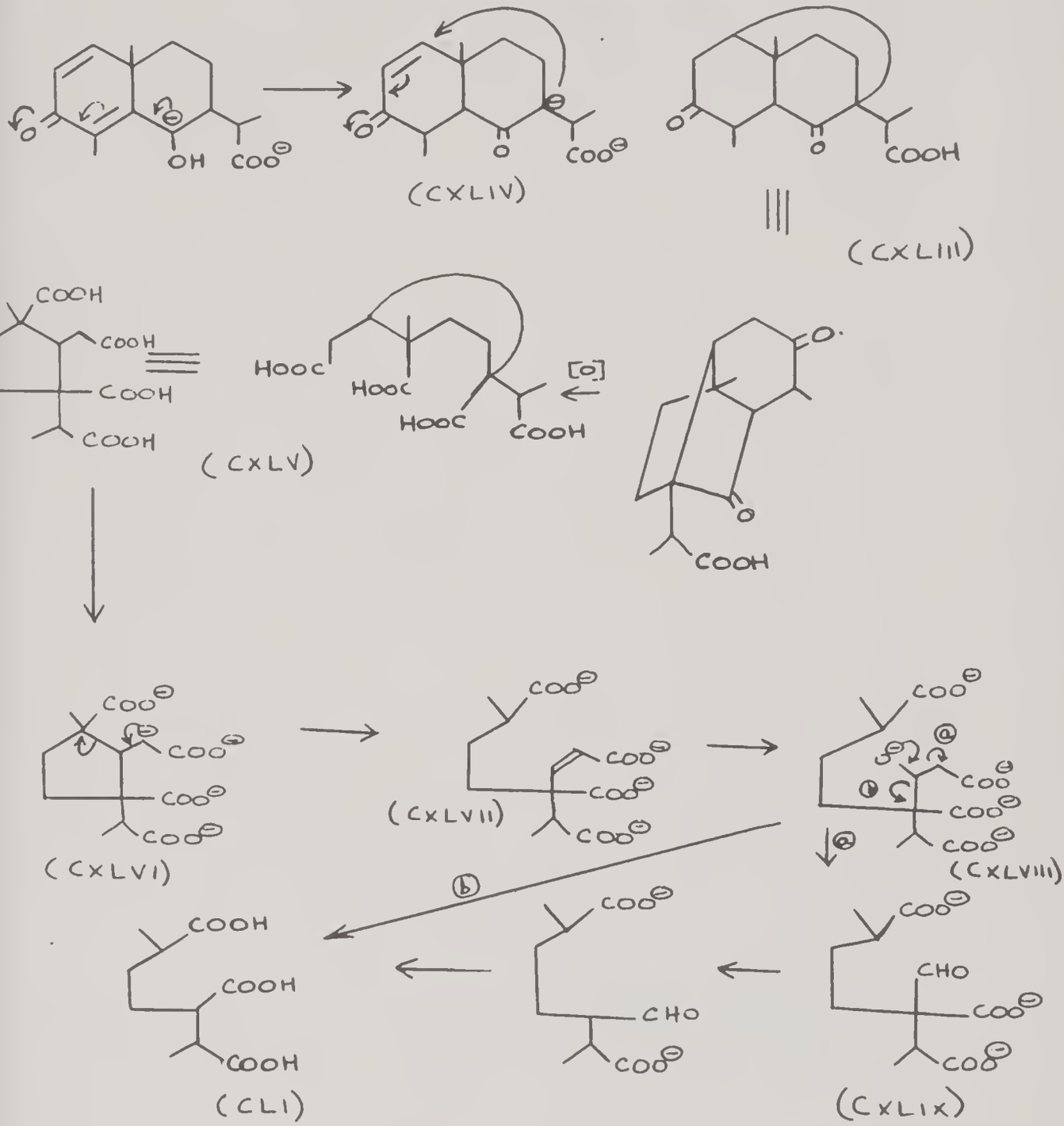


(CXXXVIII)



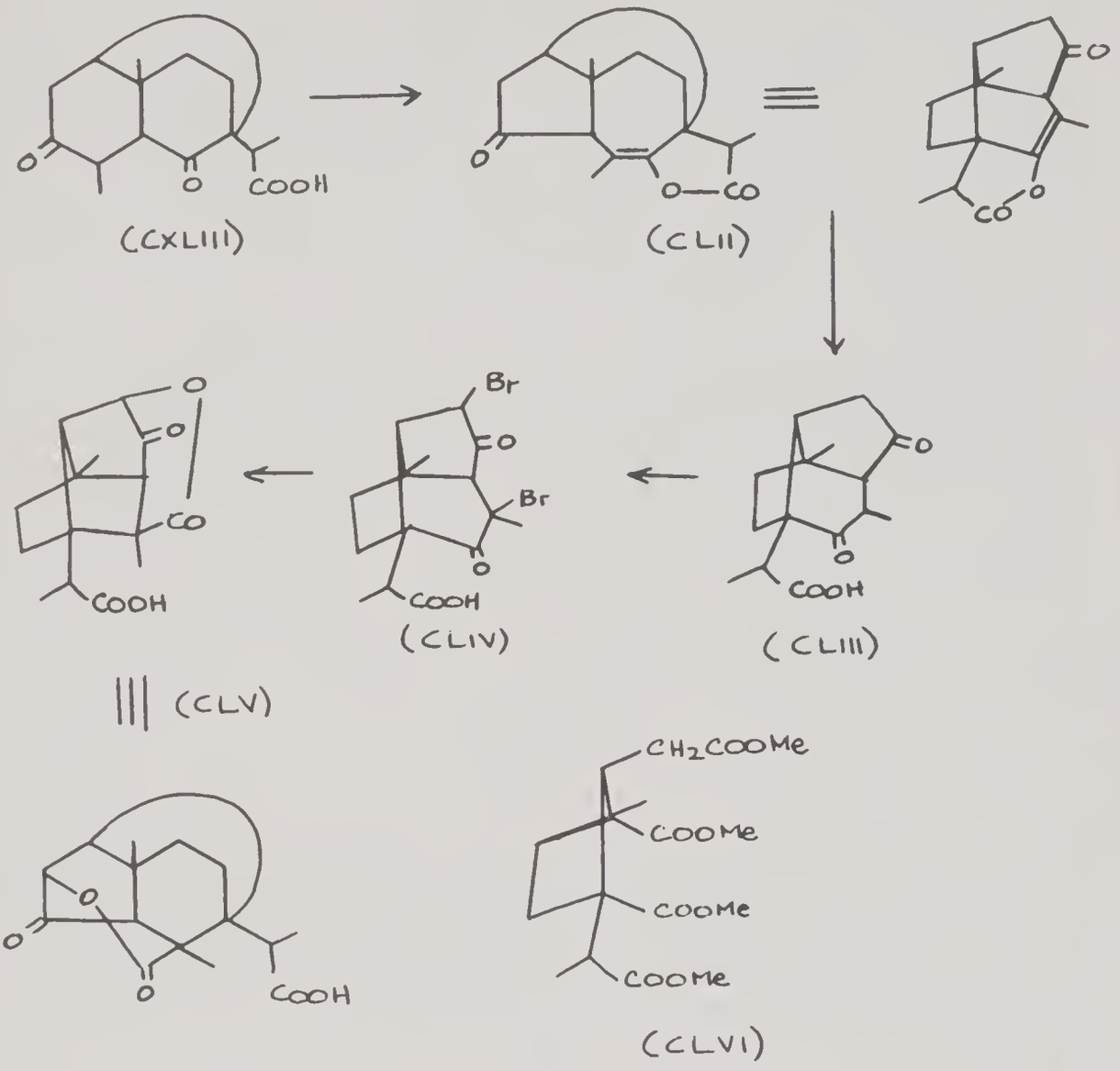
bulk of accumulated work came only in 1948 (47) and in the scheme opposite some of this is illustrated employing the formula established by Woodward and his collaborators. Santonic acid (CXLIII) is formed by the internal Michael addition of the anion of the diketone (CXLIV) on to the unsaturated ketone. Oxidation with potassium permanganate gives the tetracarboxylic acid, α-santoric acid (CXLV), and this by heating with potassium hydroxide at 300° gives α-santoronic acid (CLI). This extraordinary series of reactions, culminating in (CLI), was confirmed by the synthesis of (CLI). The conversion (CXLVI) ⟶ (CXLVII) under these drastic alkaline conditions is a reversed Michael reaction. It is then followed by hydration of the conjugated double bond and dealdolisation to the aldehyde (CXLIX). Loss of carbon dioxide (β-aldehydo acid) takes place at this point or after oxidation to the substituted malonic acid. Alternatively dealdolisation may take place directly from (CXLVIII) to (CLI).

Treatment of santonic acid with acetic acid for a prolonged period followed by heating of the residue to 260–300° gives first san-


OH
COO⊖
(CXLIV)
COOH
(CXLIII)
HOOC
[O]
(CXLV)
(CXLVI)
(CXLVII)
(CXLVIII)
(CL)
CHO
(CXLIX)

tonide, then parasantonide (CLII), substances stereoisomeric at C_{11}. The latter on hydrolysis gives parasantonic acid (CLIII), brominated in chloroform solution to dibromoparasantonic acid (CLIV) and further converted with sodium hydroxide to dehydrodihydroxyparasantonic acid (CLV), which contains four fused rings. This subtle series of changes has also been interpreted by Woodward. The structure of (CLII) was demonstrated by ozonolysis and treatment of the ozonide with methanolic hydrogen chloride when four products were isolated. One of these, (CLVI) tetramethyl β-santorate, was of known structure, being the methyl ester of a stereoisomeride of α-santoric acid (CXLV). The number of possible structures was then reduced to four and a consideration of the properties of one of the other ozonolytic compounds showed that it was a β-diketone enol ether (CLVIIb), and that parasantonide contained therefore the grouping (CLVIIa) transformed as shown. The structure of parasantonide was therefore unambiguously established as (CLII). The transformation of (CLIV) to (CLV), structures which have not been rigidly established, proceeds through the conversion of an α-halocarbonyl compound to the carboxylic acid. This is an example of the Favorski reaction (48), although it should be noted that it cannot proceed through the usual cyclopropanone intermediate, but presumably by the mechanism shown opposite, which is analogous to the benzilic acid rearrangement. A few examples are known where the Favorski reaction takes place when no carbanion, because of substitution, can be formed on C_α. The genesis of (CLII) from (CXLIII) is obscure, but a possible interpretation has been proposed (47).

Another aspect of santonin chemistry which promises to be richly rewarding is that of its photochemical transformation products. Amongst the most important of these are the substances photosantonic and *iso*photosantonic acids, obtained by exposure of santonin in different solvents to sunlight. These were investigated at the turn of the century by a group of Italian workers (50)

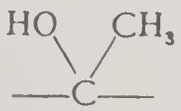


$$O{=}\overset{|}{C}-CH-\overset{|}{C}{=}C \xrightarrow{O_3} O{=}\overset{|}{C}-CH-\overset{|}{C}O \xrightarrow[HCl]{MeOH/} O{=}\overset{|}{C}-C{=}C-O-$$

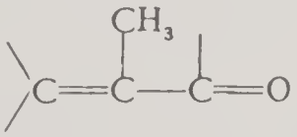
(CLVIIa) (CLVIIb)

headed by Cannizzaro and Francesconi. Formulae (CLVIII) and (CLIX) were proposed based, in the former case, on a considerable amount of excellent work. These proposed constitutions, however, contained several anomalies which became apparent when the chemistry of santonin became better known, and these substances have recently been reinvestigated (51). The structure of *iso*photosantonic acid has been shown to be (CLX).

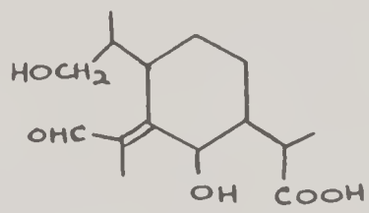
"*Iso*photosantonic acid," obtained by irradiation in aqueous acetic acid, is, in the first place, a hydrated lactone and not an acid, as has been clearly established by infra-red evidence. It is furthermore a tertiary, not a primary, alcohol, and fails to respond to characteristic tests for aldehydes. It is, in fact, an unsaturated ketone ($\lambda_{max.}$ 240 mμ). On dehydration with thionyl chloride and pyridine an anhydro compound (CLXI) is obtained which, since it gives formaldehyde on ozonolysis, must contain an *exo* methylene group. The grouping



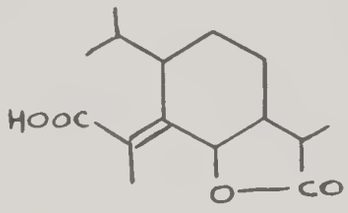
must, therefore, be present in the original substance. On ozonolysis and hydrolytic cleavage of *iso*photosantonic lactone, acetic acid and a *bis*-γ-lactone are obtained, thus establishing both the relationship of the ketone to the hydroxyl group, and the presence of the grouping



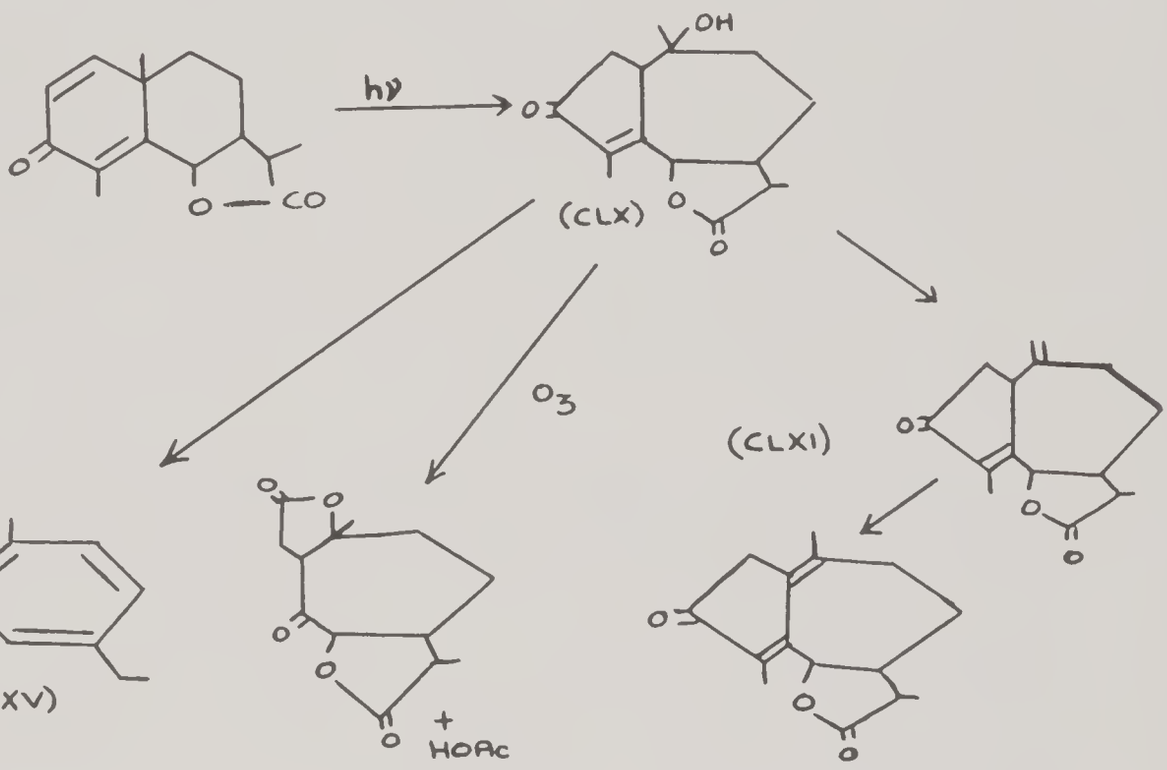
Further, the anhydro compound, by treatment with acid, could be transformed into a conjugated dienone. These facts, and others, together with the hydrogenation and subsequent dehydrogenation of *iso*photosantonic lactone to chamazulene (XV), completely established its structure. These transformations may be represented as shown opposite. A transformation closely allied to this has recently been carried out on a steroid derivative containing the same chromophore (49). The process by which santonin is transformed into



(CLIX)



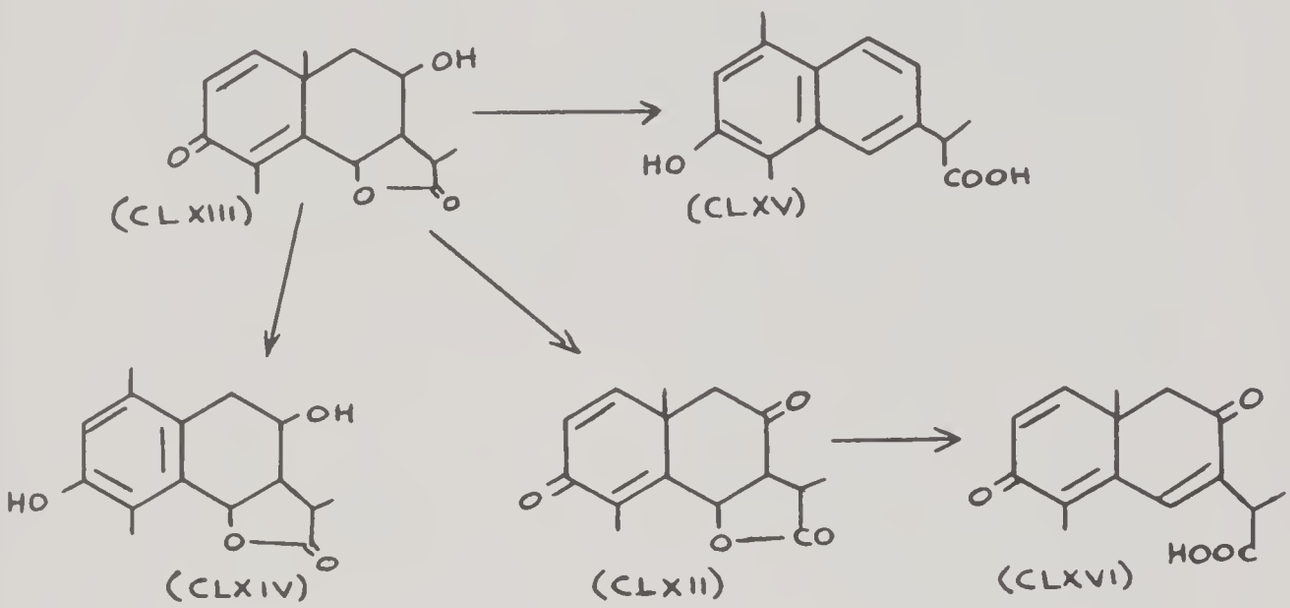
(CLVIII)

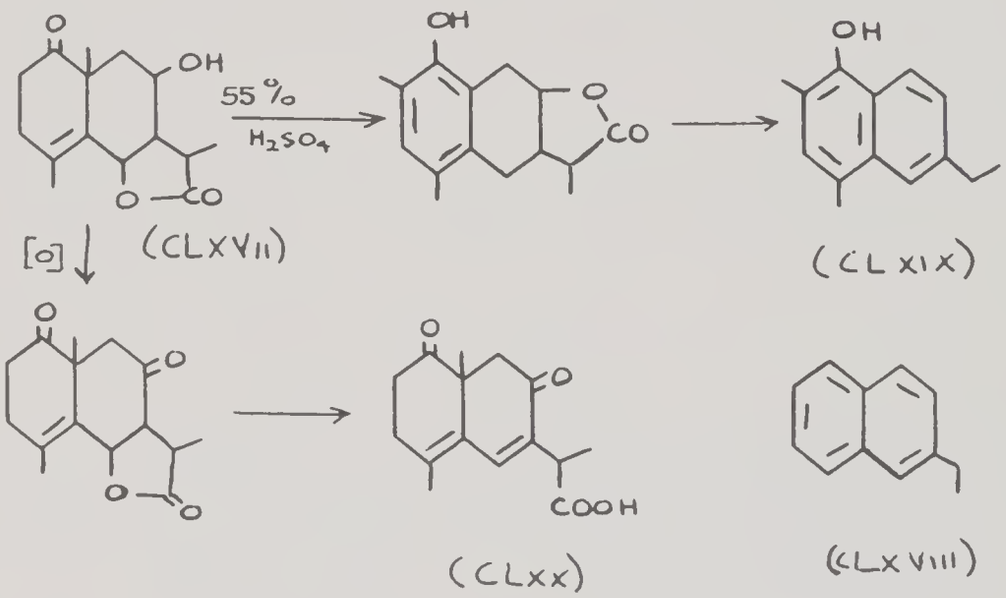


(CLX) is not yet understood, but there are indications that intermediate(s) may exist. Further work on the other irradiation products of santonin will certainly follow.

Artemesin (CLXIII) is a hydroxysantonin which has been isolated from *Artemisia maritima* and many of its reactions parallel those of santonin. With strongly acidic reagents, by rearrangement and dehydration, artemesic acid (CLXV) is obtained, whilst with dilute sulphuric acid below 60° desmotropoartemesin (CLXIV) is the product. The position of the hydroxyl group, thought once (61a) to be tertiary, has been shown recently to be secondary by oxidation to the ketone (CLXII), further converted to (CLXVI) (61b).

ψ-Santonin (CLXVII) occurs, in small amount, with santonin and other lactones in the flower heads of *Artemisia maritima*. Its reduction and dehydrogenation to noreudalene (CLXVIII) suggested a close relationship with the associated lactones. It contains a ketonic function, a hydroxyl group, and a double bond (non-conjugated) in addition to the lactone. The position of this ketonic function is suggested by the following reaction. Treatment of ψ-santonin with 55% sulphuric acid gives a desmotropo-ψ-santonin, which on palladised charcoal dehydrogenation gives (CLXIX). The probable course of this reaction is explained below. The relationship of the hydroxyl group, double bond, and lactone was shown (52) by oxidation to the diketone and elimination with base to give (CLXX). The alternative formulation (CLXXI) for ψ-santonin is excluded on the basis of the following reactions. The hydrogena-

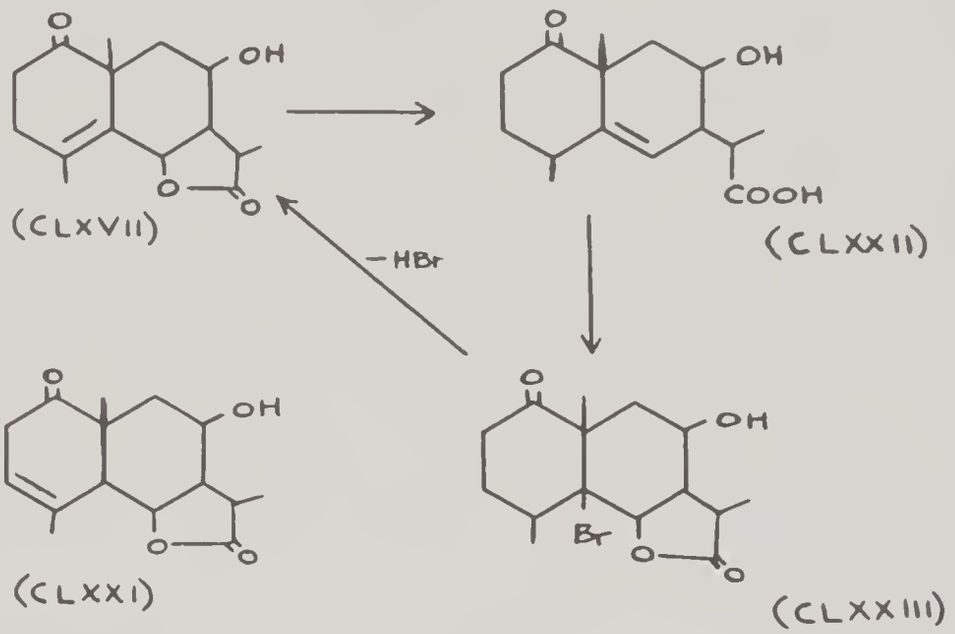

OH
O
O
O
(CLXIII)
HO
COOH
(CLXV)
HO
OH
O
O
(CLXIV)
O
O
CO
(CLXII)
O
O
HOOC
(CLXVI)

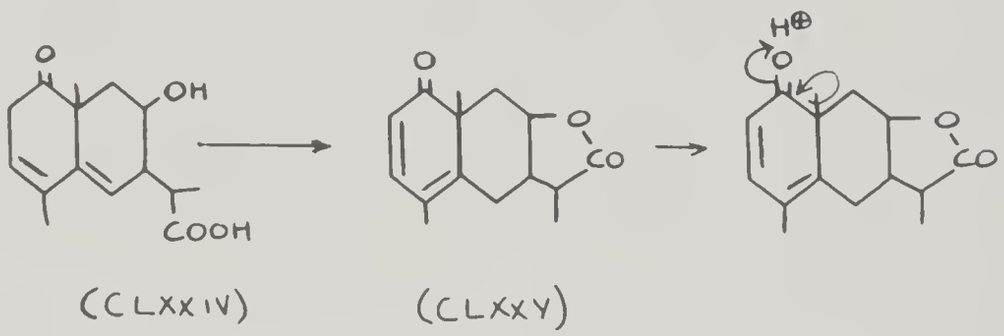

O
OH
O
CO
(CLXVII)
55 %
H2SO4
OH
O
CO
OH
(CLXIX)
[O]
O
O
O
O
COOH
(CLXX)
(CLXVIII)

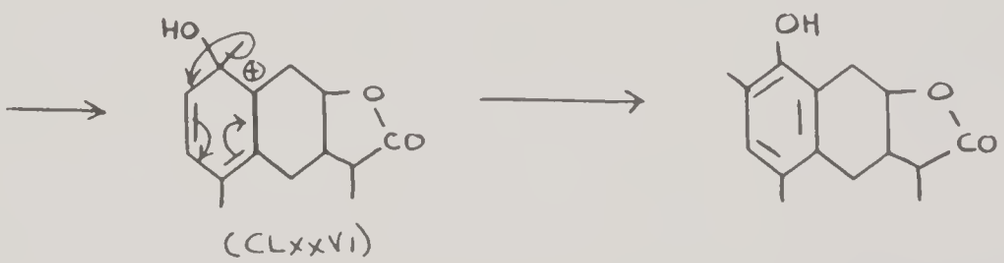
tion of (CLXVII) in acetic acid with palladised charcoal gives (CLXXII), an acid still containing a ketonic, a hydroxylic, and an ethylenic function. The cleavage was, therefore, a hydrogenolysis. The position of the ethylenic linkage was then confirmed by addition of bromine to give (CLXXIII), a bromolactone which on dehydrohalogenation gave back (CLXVII). The compounds (CLXXII, methyl ester) and (CLXVII, acetate) were examined by nuclear magnetic resonance and, whereas the latter was clear in the region where an ethylenic hydrogen would be expected to absorb, the former had a distinct band.

The first product of the reaction of ψ-santonin with acidic reagents is not desmotropo-ψ-santonin. By the action of cold concentrated hydrochloric acid, an acid, ψ-santonic acid, is obtained. It is a diene and its structure was thought to have been shown (52) by oxidation with manganese dioxide, a reagent largely specific (54) for allylic alcohols (or their equivalent), to (CLXX). Further work (53) has shown that (CLXXIV) is, in fact, correct. The aromatisation then presumably proceeds through (CLXXV) and (CLXXVI).

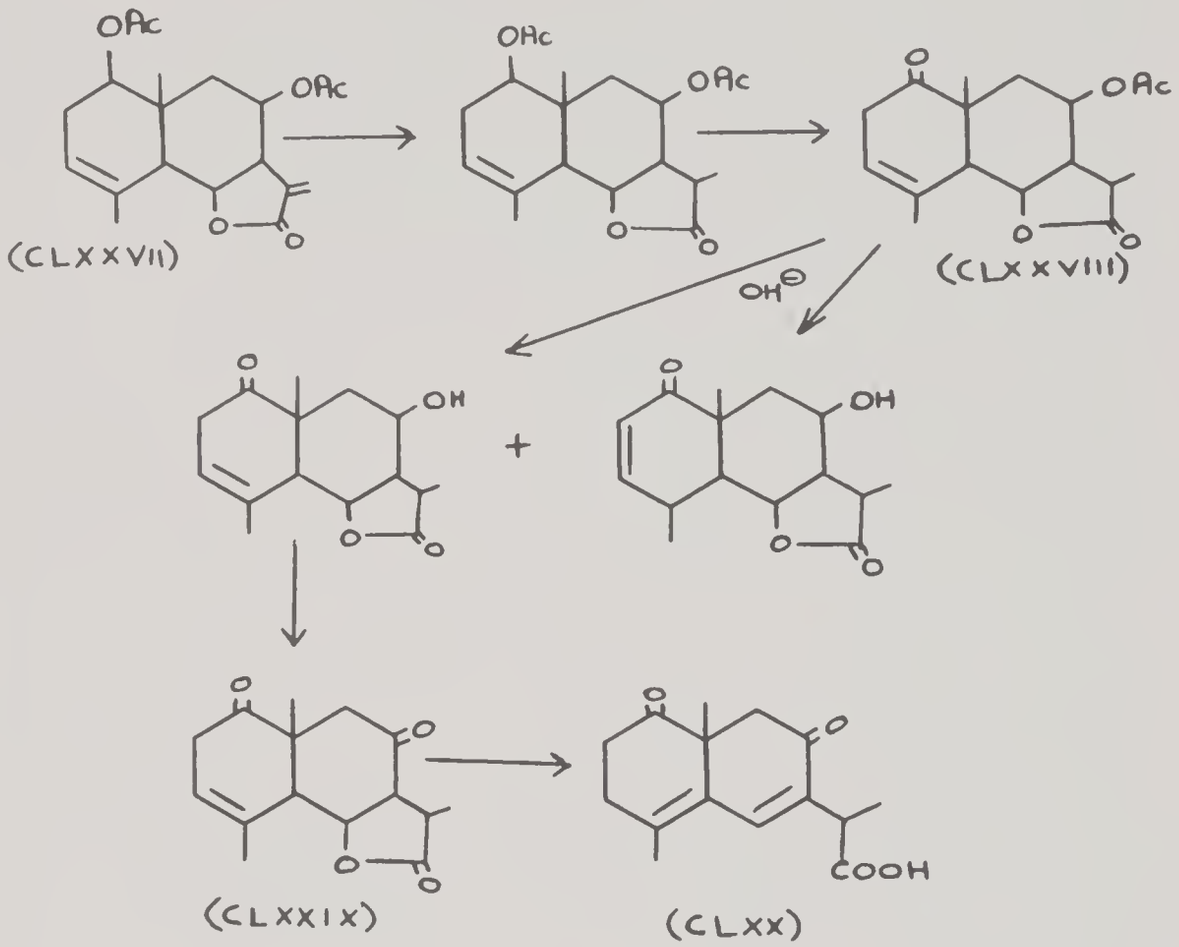
The substance **pyrethrosin** was first isolated by Thoms in 1891 from *Chrysanthemum cinerariaefolium* and its structure has recently been investigated (7). It is a monocarbocyclic lactone containing two ethylenic linkages. Five oxygen atoms are present; two as a lactone, two as an acetate, and the fifth ethereal. The latter statement is based on (a) the absence of OH-stretch in the infra-red, (b) equilibration with deuterium oxide causing the introduction of no deuterium, and (c) recovery unchanged on mild acetylation. However, in contradiction, previous workers had indicated the formation of a "dehydropyrethrosin" by the action of chromic acid. Of the two ethylenic linkages, one was conjugated with the lactonic carbonyl, as indicated by the ultra-violet absorption spectrum. Formaldehyde was obtained on ozonolysis.

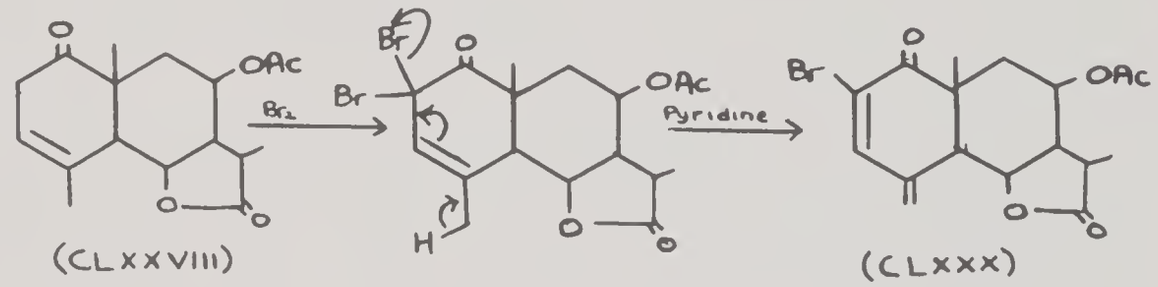

OH
COOH
-HBr
Br
(CLXVII)
(CLXXII)
(CLXXI)
(CLXXIII)

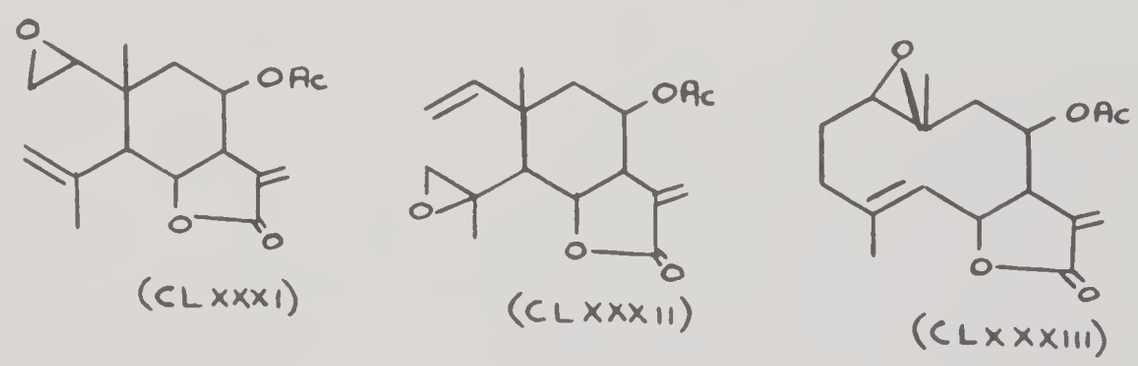

OH
COOH
CO
H⊕
(CLXXIV)
(CLXXV)


HO
⊕
CO
OH
(CLXXVI)

On heating with acetic anhydride–toluenesulphonic acid, pyrethrosin was cyclised to give *cyclo*pyrethrosin acetate (CLXXVII) and the structure of this compound was determined essentially as indicated in the scheme opposite. The compound (CLXXIX) was not a conjugated ketone but on treatment with base gave (CLXX), the conjugated dienone also obtained from ψ-santonin. The position of the ethylenic linkage in (CLXXVIII) was confirmed by bromination and dehydrobromination to give the bromodienone (CLXXX) (λ_{max} 287 mμ). The formation of *cyclo*pyrethrosin acetate from pyrethrosin itself involves the opening of the ethereal ring by acetylium ion and formation of a new carbon–carbon bond by participation of the ethylenic linkage. On the assumption that the introduced acetate in (CLXXVII) marks one end of the oxide ring or double bond in pyrethrosin a number of possible structures may be written for pyrethrosin, e.g., (CLXXXI), (CLXXXII), and (CLXXXIII). Since dihydropyrethrosin, in which the conjugated double bond—that is, the double bond *not* involved in cyclisation—is saturated, gives no formaldehyde or other volatile aldehyde on ozonolysis, all but (CLXXXIII) may be excluded. However, the conditions of cyclisation are of such vigour as not to preclude drastic rearrangement. An examination of the oxidation products of pyrethrosin provided the required confirmation. Under mild conditions—sodium dichro-

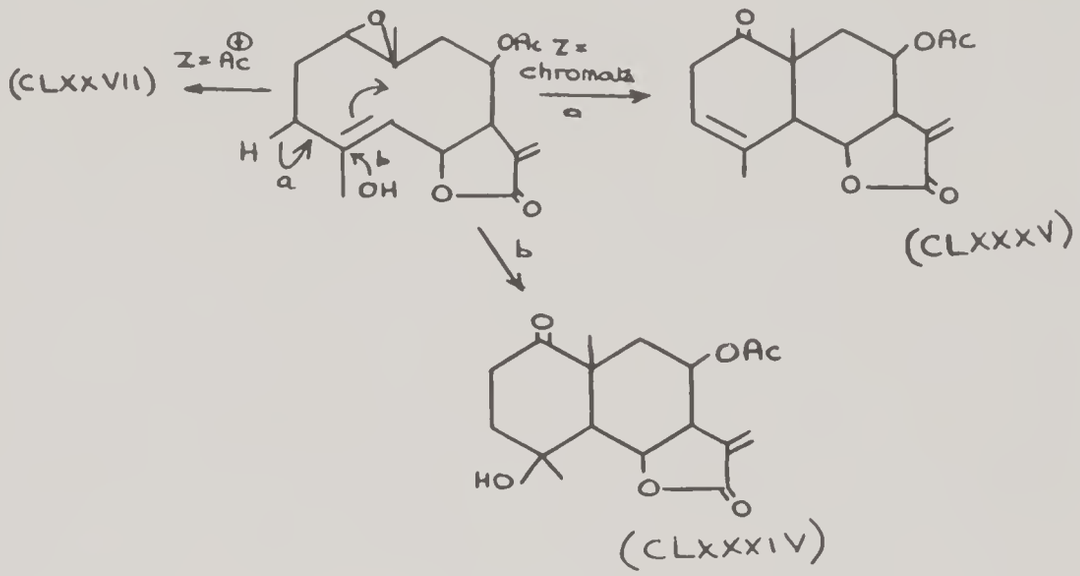

OAc
OAc
(CLXXVII)
OAc
OAc
OAc
(CLXXVIII)
OH⊖
OH
+
OH
(CLXXIX)
COOH
(CLXX)

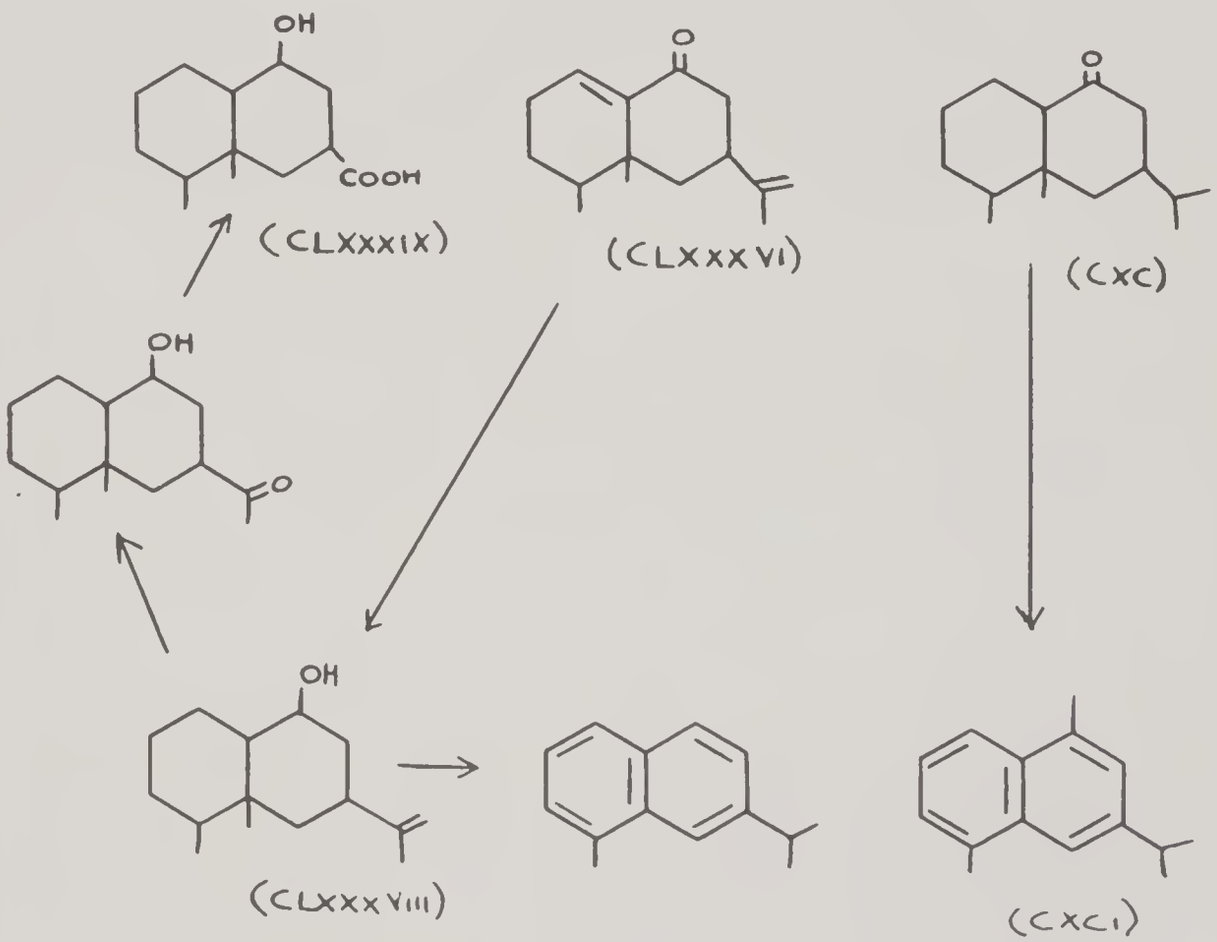

OAc
(CLXXVIII)
Br₂
Br
Br
H
OAc
Pyridine
Br
OAc
(CLXXX)


OAc
(CLXXXI)
OAc
(CLXXXII)
OAc
(CLXXXIII)

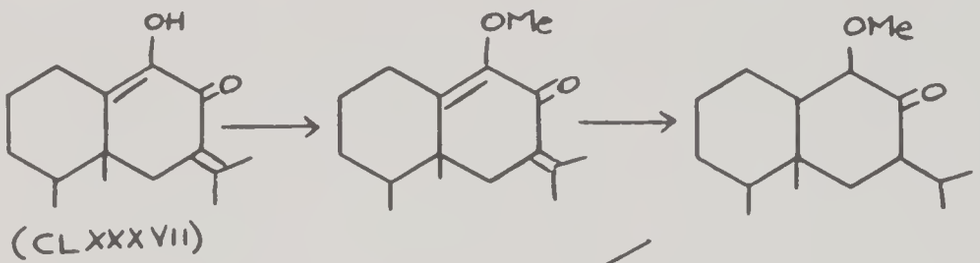
mate in acetic acid—two compounds were obtained. One (CLXXXV) on hydrogenation was converted to (CLXXVIII) whilst the other was the tertiary alcohol (CLXXXIV). The "dehydropyrethrosin" (CLXXXV) is, in fact, a cyclised product and the conditions of its genesis are so mild as to minimise the possibilities of rearrangement. This cyclisation may be rationalised as shown, where Z represents either acetylium ion or a chromate residue; in the latter case the chromic ester formed is converted to ketone in the usual way. If the proton is eliminated (course *a*), then (CLXXXV) is formed; whilst if, instead, there is attack of hydroxyl ion (course *b*), (CLXXXIV) is the product. The hydroxyl group in (CLXXXIV) marks one end of the ethylenic linkage in pyrethrosin, whilst the carbonyl group marks one end of the oxide bridge. Since (CLXXXI) and (CLXXXII) are excluded, the centre bond must be that formed, marking, therefore, the other terminus of the oxide bridge. The facility with which pryethrosin is cyclised is in itself a powerful argument for a ten-membered ring, a size of ring in which it is well known that the proximity of opposite sides of the ring may result in *trans*-annular reactions under the mildest conditions (56). These facts establish the gross structure of pyrethrosin, though possibly the positions of the acetate and lactone termination may require reversal. Pyrethrosin is so far unique amongst terpenoids as to its ring size and falls between caryophyllene, with nine, and humulene, with eleven-membered carbon rings.

The structures of **eremophilone** (CLXXXVI) and the related hydroxyeremophilone (CLXXXVII), both found in the wood oil from *Eremophila mitchelli*, are of particular interest since they present exceptions to the isoprene rule—i.e., their structures cannot be built up from three *iso*pentane residues (57). Eremophilone is an α:β-unsaturated ketone, as shown by its ultra-violet spectrum and by reduction with sodium and alcohol to dihydroeremophilol (CLXXXVIII). The latter, on dehydrogenation, gives eudalene. The position of the other ethylenic linkage was shown by ozonisation of (CLXXXVIII) to a methyl ketone oxidised with hypobromite to the corresponding acid (CLXXXIX). The position of the ketonic function was demonstrated by treatment of (CXC) with methyl magnesium iodide, and dehydrogenation to (CXCI). Since eremophilone

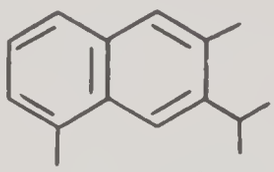

(CLXXVII)
Z = Ac
OAc
Z = chromate
a
H
a
b
OH
b
OAc
(CLXXXV)
OAc
HO
(CLXXXIV)


OH
COOH
(CLXXXIX)
(CLXXXVI)
(CXC)
OH
OH
(CLXXXVIII)
(CXCI)

contained a methylene group adjacent to the carbonyl group (formation of a hydroxymethylene derivative), the angular group could not be in the usual position. This appeared remarkable because at the time this work was carried out no exception to the isoprene rule was known. Evidence as to the position of this angular methyl group was obtained as follows. On treatment with hydrogen peroxide eremophilone gives an oxide which by heating with sodium acetate in acetic anhydride, followed by hydrolysis, gave hydroxyeremophilone (CLXXXVII). The position of the carbonyl group in this substance was shown by successive methylation, hydrogenation, reaction with methylmagnesium iodide, and dehydrogenation to (CXCII). Hydroxyeremophilone benzoate, on ozonolysis, gave acetone, indicating the presence of the *iso*propylidene group, and, amongst other products, a monocyclic keto acid (CXCIII). Clemmensen reduction gave (CXCIV), the structure of which was shown by synthesis, and this fragment contains the missing angular methyl group. The conversion of eremophilone epoxide (CXCV) into (CLXXXVIII) may possibly be represented by the stages shown, where $Ac^{\oplus}$ refers to the polarised acetic anhydride molecule. Hy-

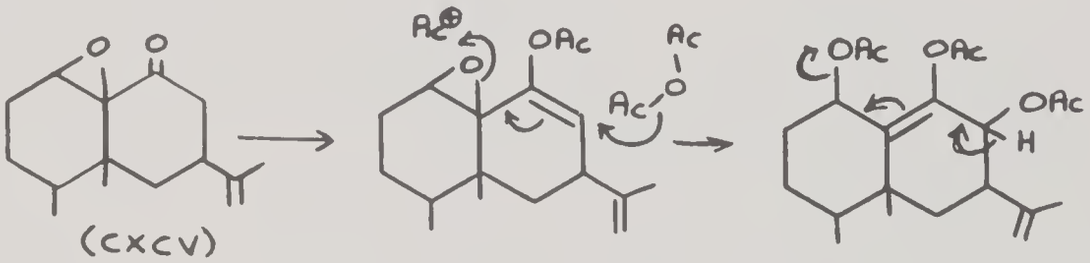


(CLXXXVII)

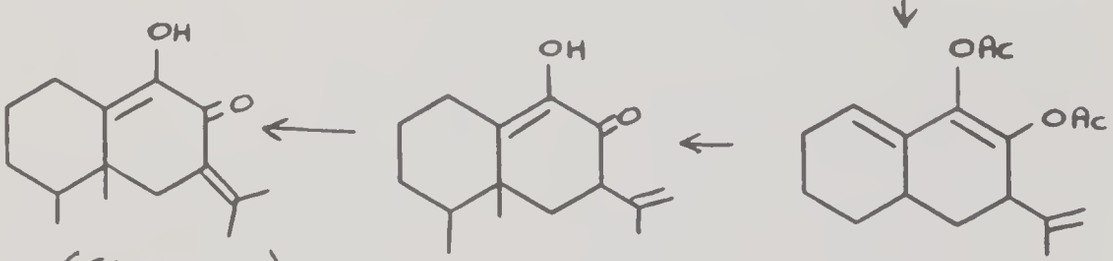


(CXCII)

(CXCIII) (CXCIV)



(CXCV)



(CLXXXVIII)

droxydihydroeremophilone (CXCVI), which also occurs naturally, has been the subject of X-ray analysis (58). It has the stereochemistry indicated. It is unusual in being a derivative of *cis*-decalin, the substituent groups being in the more stable equatorial position. It has been suggested that eremophilone itself might arise by dehydration and rearrangement of such an isoprenoid precursor as (CXCVII) which might then have the same stereochemistry as the cyperones. Its absolute configuration, as supported by a combination of X-ray and molecular rotation arguments (34), was believed to be as in (CXCVIIIa). Very recent work by Djerassi and his colleagues (36) has shown, on the basis of rotatory dispersion measurements, that the absolute configuration must be reversed as in (CXCVIIIb). This illustrates the dangers of allocating a configuration based on the rotation at a single wavelength, rather than on the whole curve.

Amongst the compounds not discussed may be mentioned the alantolactones (CXCIX) (55), sesquibenihiol (CC), α-santalene (CCI), β-santalene (CCII), and the related alcohols (CCIII) and (CCIV) for which the structures shown have been proposed.

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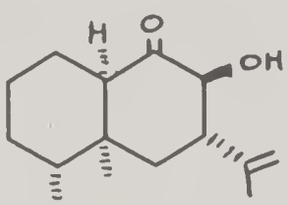
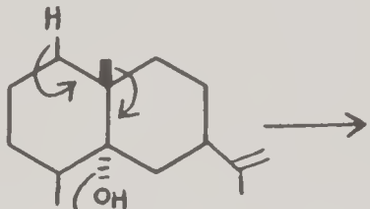
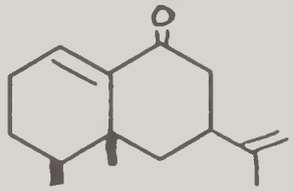


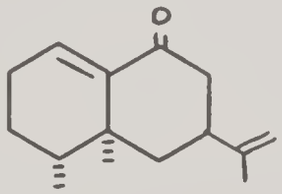
(CXCVI)



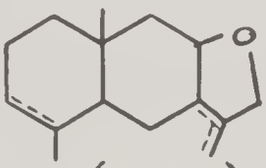
(CXCVII)



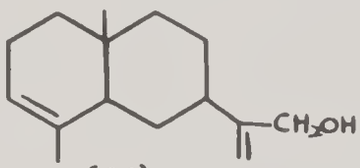
(CXCVIIIa)



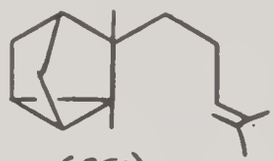
(CXCVIIIb)



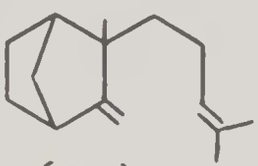
(CXCIX)



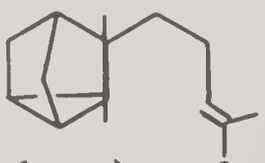
(CC)



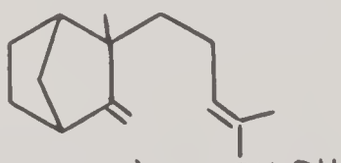
(CCI)



(CCII)



(CCIII)



(CCIV)

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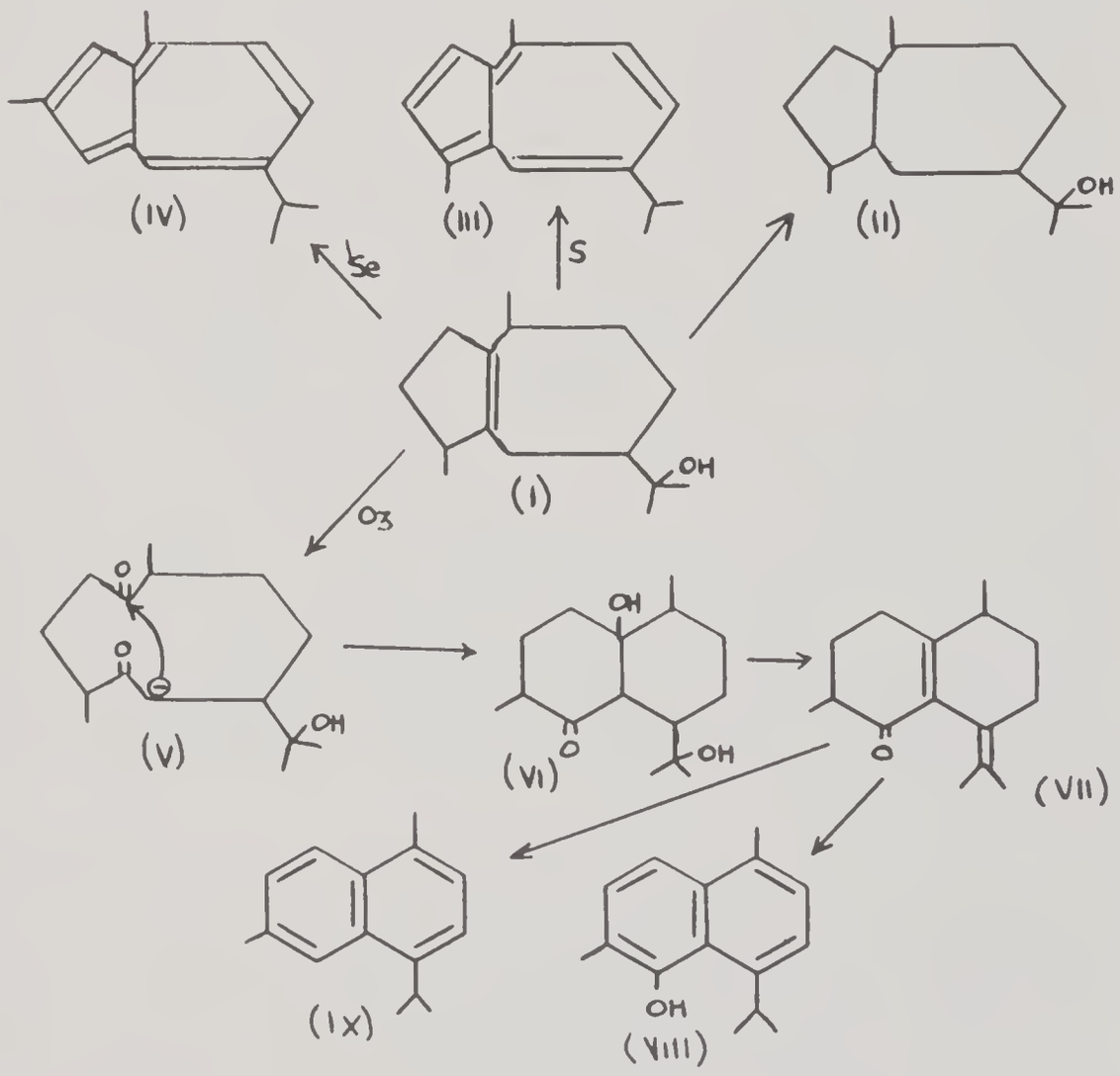
THE SESQUITERPENOIDS: II. THE AZULENIC SESQUITERPENOIDS

The basic azulene skeletons common to this group of substances have already been illustrated (page 183). By far the greater number of known azulenic sesquiterpenoids have structures based on guaiazulene. For convenience of description only, these azulenic derivatives may be divided into two groups depending on whether the substance does or does not contain a lactone (or more rarely a carboxyl group).

THE NON-LACTONIC GROUP

From guaiacum wood oil an alcohol, **guaiol** (I), was first isolated in 1892. It was shown to be a tertiary alcohol by its resistance to acylation and by its ease of dehydration. Guaiol also contained an ethylenic linkage which was very resistant to hydrogenation, but under pressure, in the presence of Raney nickel, it could be hydrogenated to dihydroguaiol (II). With sulphur, dehydrogenation afforded S-guaiazulene (III), but with selenium, possibly because of the higher temperature, Se-guaiazulene, largely (IV), was obtained (1).

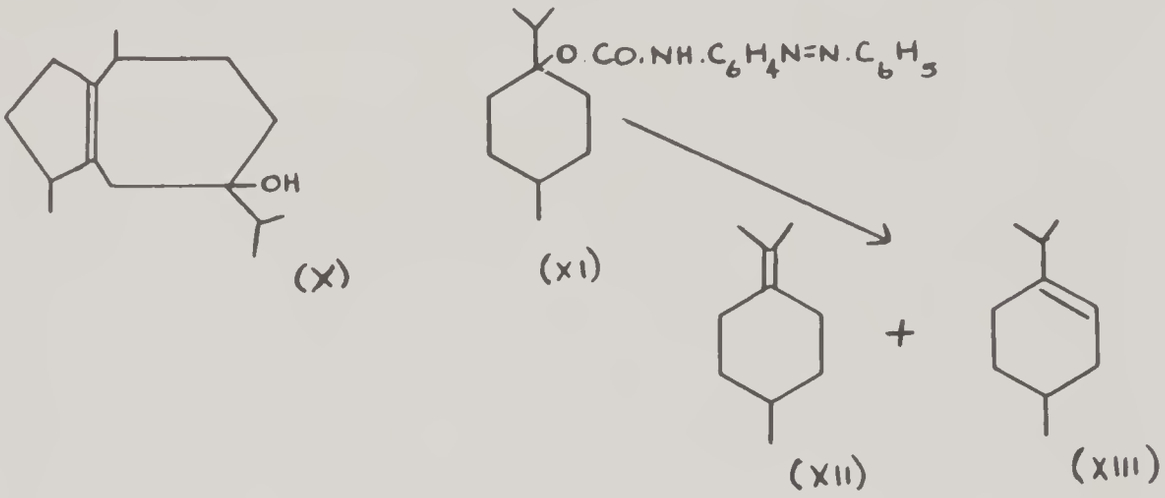
Some further evidence as to the structure of guaiol was obtained by ozonolytic degradation of the dehydration product of dihydroguaiol. The most important information, however, came as follows (2). The diketone (V) cyclises by an internal aldol condensation to form (VI) which by β elimination of one hydroxyl group and dehydration of the other gives the cross-conjugated dienone (VII). By dehydrogenation of (VII) under varying conditions cadalene (IX) or the re-


(IV)
(III)
(II)
OH
Se
S
(I)
OH
O3
O
O
(V)
OH
OH
(VI)
O
OH
O
(VII)
(IX)
OH
(VIII)

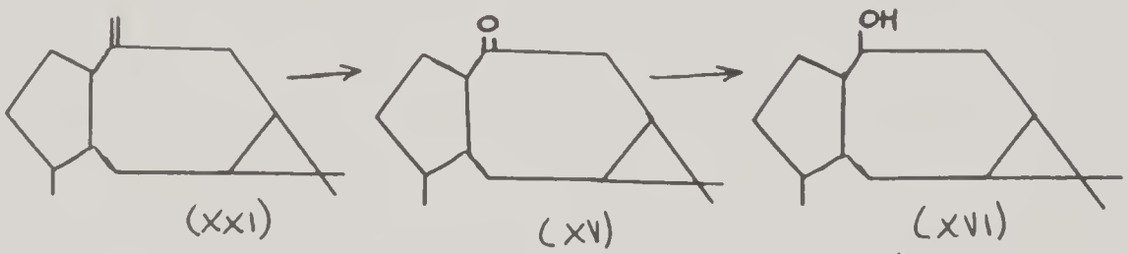
lated naphthol was obtained. Whilst these reactions certainly fixed the position of the double bond, the alternative formula (X), differing in the position of the hydroxyl group, remained as a possibility for guaiol, and indeed might better explain such results as the very ready elimination of the second hydroxyl group (which would then also be β to the ketone) in the change from (VI) to (VII). This possibility has now been excluded (3) by the results of pyrolysis of the phenylazophenylurethane of guaiol. The products obtained are aminoazobenzene and a mixture of hydrocarbons. The latter showed, in its infra-red spectrum, bands at 1643 and 887 cm^{-1} characteristic of the grouping $CR_2 = CH_2$. Since, under the conditions of the experiment, a double bond, once formed, would not be expected to migrate, the position of the hydroxyl group in guaiol is fixed. In confirmation model experiments performed on terpinen-4-ol phenylazophenylurethane (XI) gave a mixture of hydrocarbons, presumably (XII) and (XIII), showing no such bands.

Aromadendrene is the principal sesquiterpenoid hydrocarbon occurring in eucalyptus oils. It is easily reduced by catalytic hydrogenation, with uptake of one molecule of hydrogen to give the saturated dihydroaromadendrene. Since the original hydrocarbon has the formula $C_{15}H_{24}$, it is therefore tricyclic, and its basic skeleton was shown by dehydrogenation to give guaiazulene. The third ring, easily opened by the action of acidic reagents, was presumed to be *cyclo*propane in type. The position of the double bond in the hydrocarbon was shown by ozonolysis to give a ketone, *apo*aromadendrone (XV), reduced to the corresponding alcohol (XVI) by sodium and alcohol. This, on dehydration with boric acid (4), gave *apo*aromadendrene (XVII) which on dehydrogenation gave an azulene, said to be (XIV), in which the methyl group at C_4 in guaiazulene has disappeared. The position of the original methylene group is therefore clear.

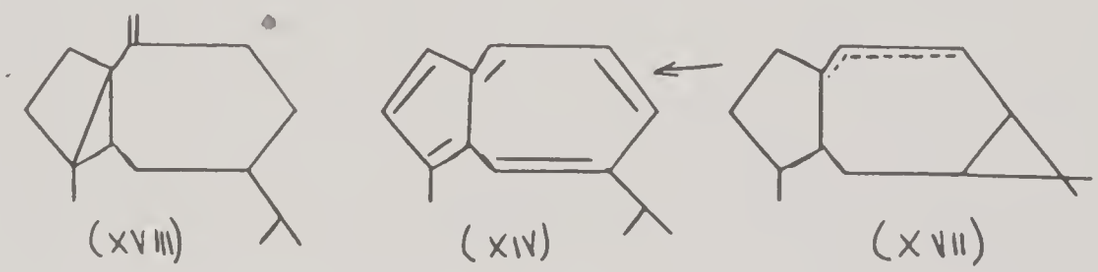
On the basis of this and other evidence Treibs and Barchet (4) proposed the structure (XVIII). Reinvestigation (5) has now shown that (XIX) cannot be the structure of *apo*aromadendrone as would be expected on the basis of the structure (XVIII). The ketone group is, in fact, adjacent to an epimerisable centre because an alkalilabile isomer of *apo*aromadendrone has now been prepared which is



(X) (XI) (XII) (XIII)



(XXI) (XV) (XVI)



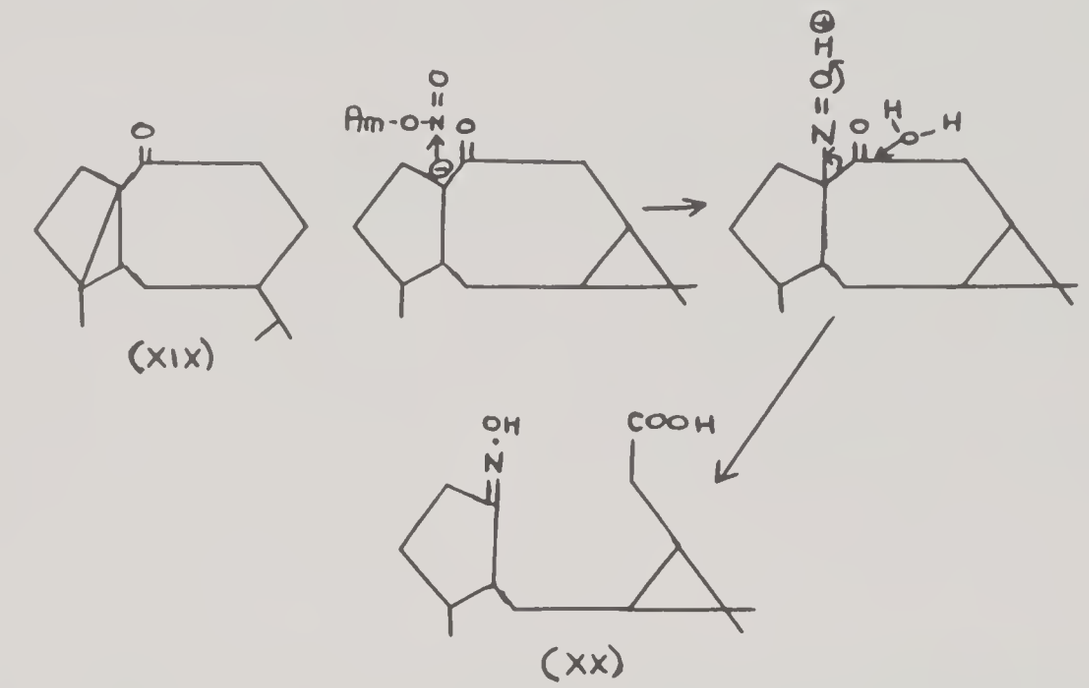
(XVIII) (XIV) (XVII)

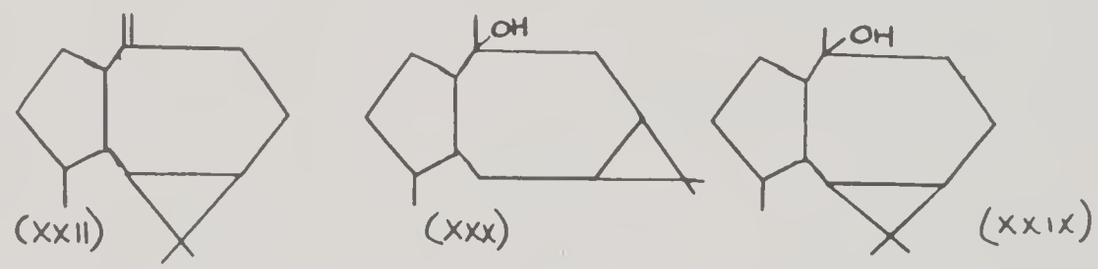
easily converted into the previously known more stable form. Further, by reaction with amyl nitrite and acid, an oximino acid (XX) has been obtained.

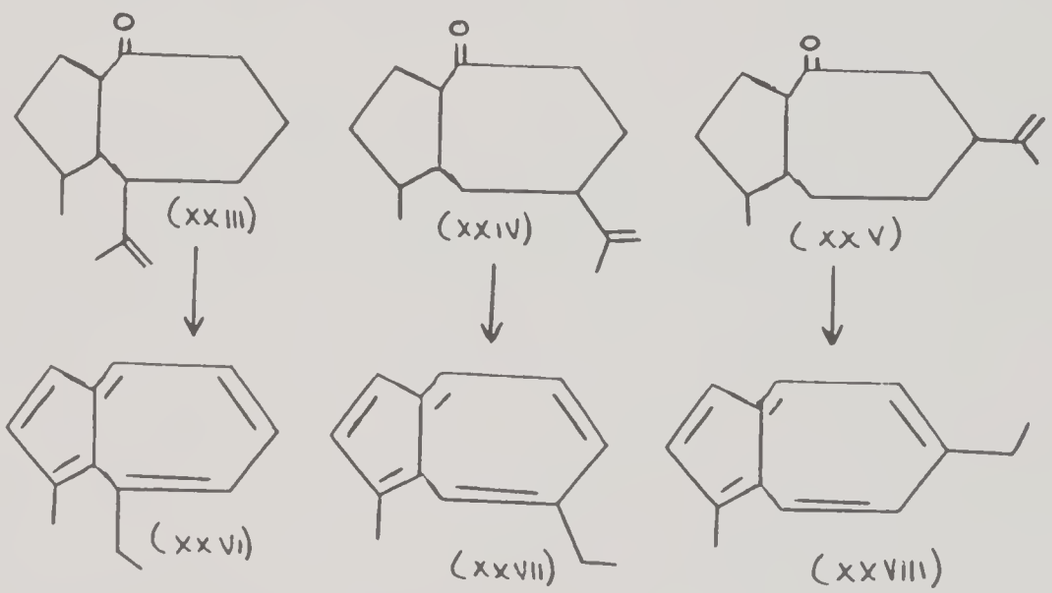
This oxime on hydrolysis gave a ketone the infra-red of which indicated that the carbonyl was in a five-membered ring. Structures (XXI) or (XXII) have thus been proposed as possible structures for aromadendrene. On treatment with hydrogen chloride the *cyclo*propane ring in *apo*aromadendrone is cleaved with the generation of a new exocyclic methylene group. On the basis of Markownikoff cleavage of structures related to (XXII) and (XXI), (XXIII) and (XXIV) or (XXV) might be expected. Ozonolysis, followed by reduction of the ketones so formed to the alcohols, dehydration, and, finally, dehydrogenation could give the azulenes, (XXVI) or (XXVII), (XXVIII). The product obtained is said (4) to be 7-*iso*propyl azulene, but further investigation is necessary.

The tertiary alcohol **globulol** was first isolated in 1904 by Schimmel and Co. from *Eucalyptus globulus* oil. It has recently been isolated again (6). On sulphur dehydrogenation it gives guaiazulene, and its relationship to the azulene family of sesquiterpenoids was shown by pyrolysis of the derived 3 : 5-dinitrobenzoate. At the melting point this decomposes to give 3 : 5-dinitrobenzoic acid and aromadendrene. Accepting the proposed formulae (XXI) and (XXII) for this substance the formulae (XXIX) or (XXX) follow for globulol.

Patchouli alcohol was originally isolated by Gal in 1869 from the leaves of *Pogostemon patchouly* var. *suavis*. It was then investigated by Gadamer, by Semmler and Wallach, and, later, by Treibs (7). The last-named author showed that this saturated tertiary alcohol gave on acid-catalysed dehydration a mixture of hydrocarbons —"patchoulene"—which on dehydrogenation afforded guaiazulene. The same mixture on ozonolysis and oxidation with permanganate

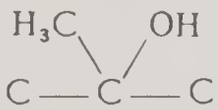

Am-O-N=O
N=O-H
COOH
OH
N
(XIX)
(XX)


OH
OH
(XXII)
(XXX)
(XXIX)


(XXIII)
(XXIV)
(XXV)
(XXVI)
(XXVII)
(XXVIII)

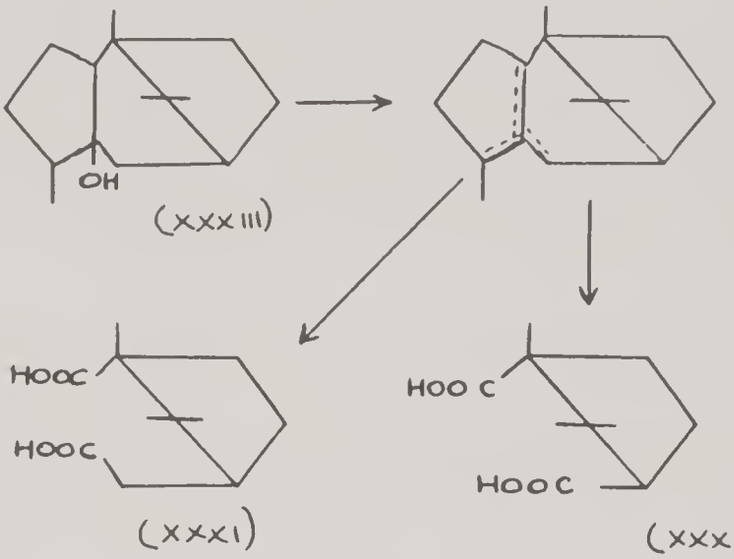
gave both homocamphoric acid (XXXI) and camphoric acid (XXXII); from this and other work Treibs deduced the structure (XXXIII) for the alcohol.

Reinvestigation by Büchi and Erickson (8) has shown the dangers involved in the deduction of structures when vigorous acid treatment is involved. Pyrolysis of patchouli alcohol acetate (prepared by the action of ketene) gave a mixture of the two hydrocarbons (XXXIVa) and (XXXIVb). Both were converted into diols by the action of osmium tetroxide. One was cleaved with lead tetraacetate to give the norketone (XXXV), demonstrating that the original hydroxyl group had the environment

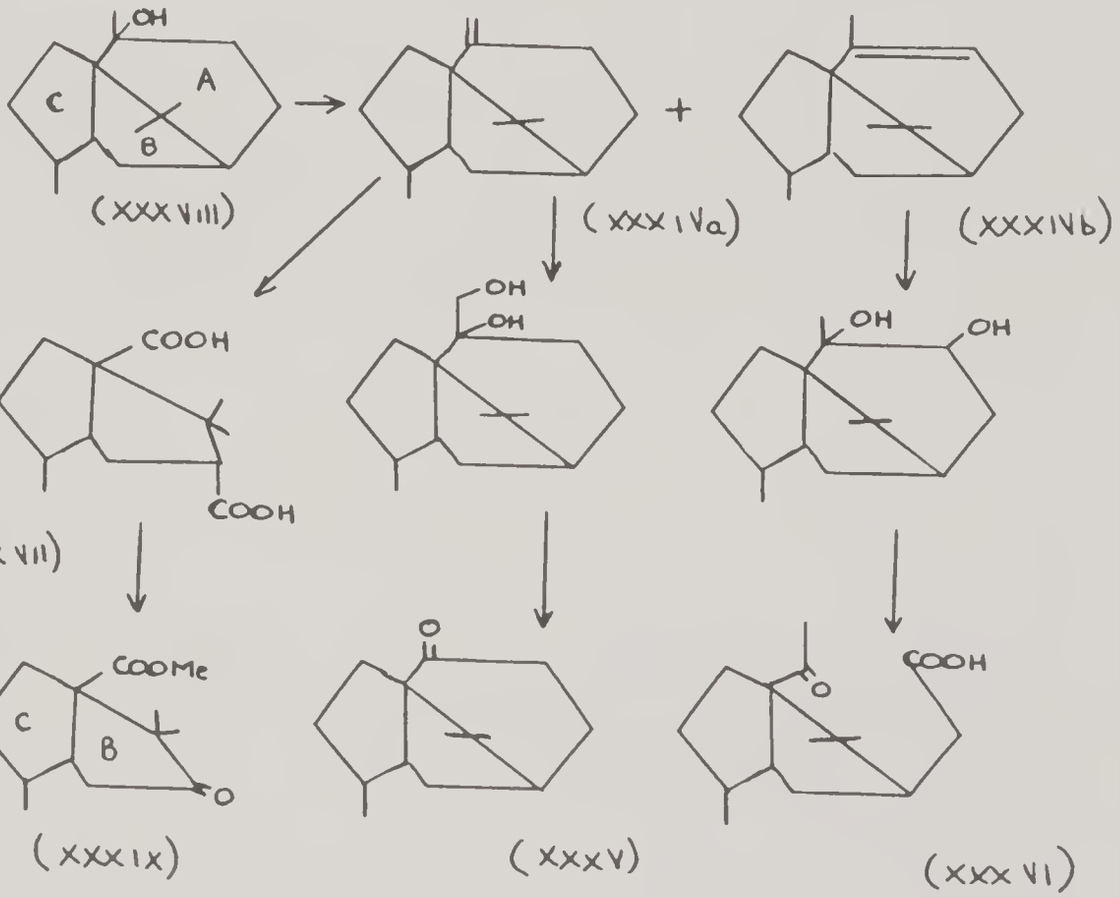


The other gave a keto acid (XXXVI). Oxidation of the hydrocarbon mixture with permanganate and nitric acid gave a dicarboxylic acid (XXXVII) the anhydride of which, from its infra-red spectrum (bands at 1786 and 1745 cm^{-1}), was shown to be a glutaric acid derivative. Ring A (formula XXXVIII) was therefore six-membered. Conversion of the dicarboxylic acid to the ester and reaction with phenylmagnesium bromide, followed by dehydration of the carbinol and subsequent ozonolysis, gave the keto ester (XXXIX). This showed in its infra-red spectrum a band at about 1730 cm^{-1} and indicated that it was in a five-membered ring. Ring B (formula XXXVIII) was therefore five-membered.

These experiments demonstrate that during the formation of Treibs' "patchoulene" rearrangement has taken place. This was initiated by the carbonium ion formed during the dehydration and was followed by a 1:2 shift. This "patchoulene," consisting



(XXXIII) (XXXI) (XXXII)



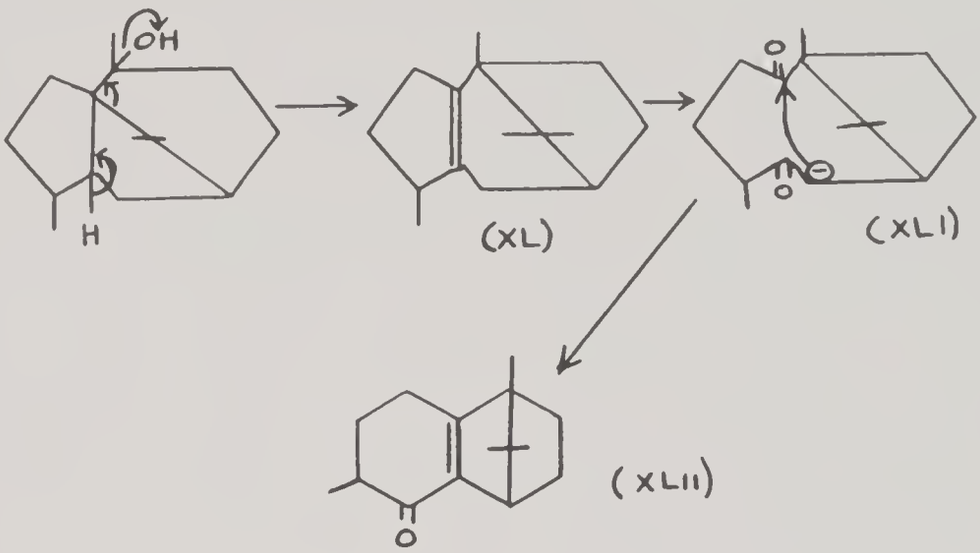
(XXXVIII) (XXXIVa) (XXXIVb)

(XXXVII) (XXXIX) (XXXV) (XXXVI)

mostly of (XL), was converted to the diol and cleaved to give the diketone (XLI) which gave a negative iodoform test. Treatment of the diketone with base, as in the parallel reaction with guaiol, led to the cyclisation and the formation of the *cyclo*hexenone (XLII). The diketone (XLI) was therefore a 1 : 5 diketone and it follows that ring C (formula XXXVIII) is also five-membered, thus completing the proof of structure.

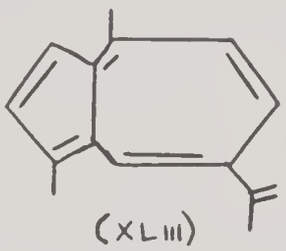
From the orange agaric (*Lactarius deliciosus*) Willstaedt (9) isolated, in 1935, a red-violet azulene which had the composition $C_{15}H_{14}O$. This formula requires that the molecule contain nine double bond equivalents and two of these are accounted for as rings. Also present in the same mushroom was a hydrocarbon azulene, lactarazulene. The first substance, **lactaroviolin,** was shown to be an aldehyde (12) by hydrogenation to the saturated alcohol, $C_{15}H_{27}OH$, which gave a trityl (triphenylmethyl) ether. It formed a semicarbazide and decomposition of this with sodium ethoxide (Wolff-Kishner) gave lactarazulene. Lactarazulene itself was shown to be (XLIII) by partial hydrogenation, with the uptake of one molecule of hydrogen, to give guaiazulene. Further, lactarazulene gave formaldehyde on ozonolysis and showed bands in the infra-red (at 887 and 1650 cm^{-1}) characteristic of the grouping $CR_2 = CH_2$. Three structures for lactaroviolin, (XLIV), (XLV), and (XLVI), were then possible.

Of these (XLIV) was excluded on the basis of polarographic reduction potentials. Decision between the other two was reached in two ways (10,11). One group of workers converted the aldehyde into the carbinol (XLVIII) by a Grignard reaction, and this was then hydrogenated with a palladised charcoal catalyst deactivated with quinoline. In this reaction both partial hydrogenation and hydrogenolysis takes place, and the final product is the ethyl derivative (XLIX). This was identified by comparison with authentic synthetic specimen. The same conclusion was reached from a knowledge of the effect of electron-attracting and electron-releasing substituents on the spectral behaviour of azulenes, and from a comparison of the observed spectrum with that of azulenes known to be substituted in the 1 position. From a theoretical standpoint it was predicted on the basis of zero-order MO calculations that a strong

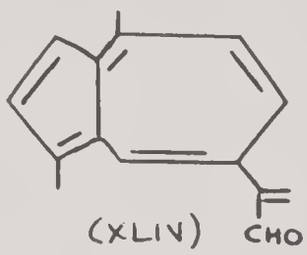


(XL) (XLI)

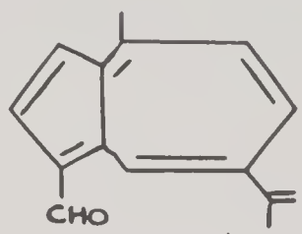
(XLII)



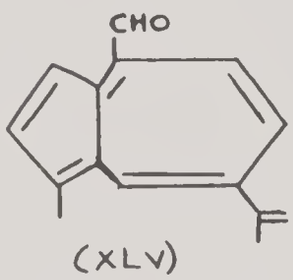
(XLIII)



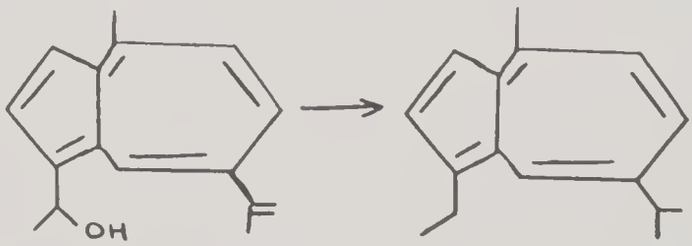
(XLIV)



(XLVI)



(XLV)

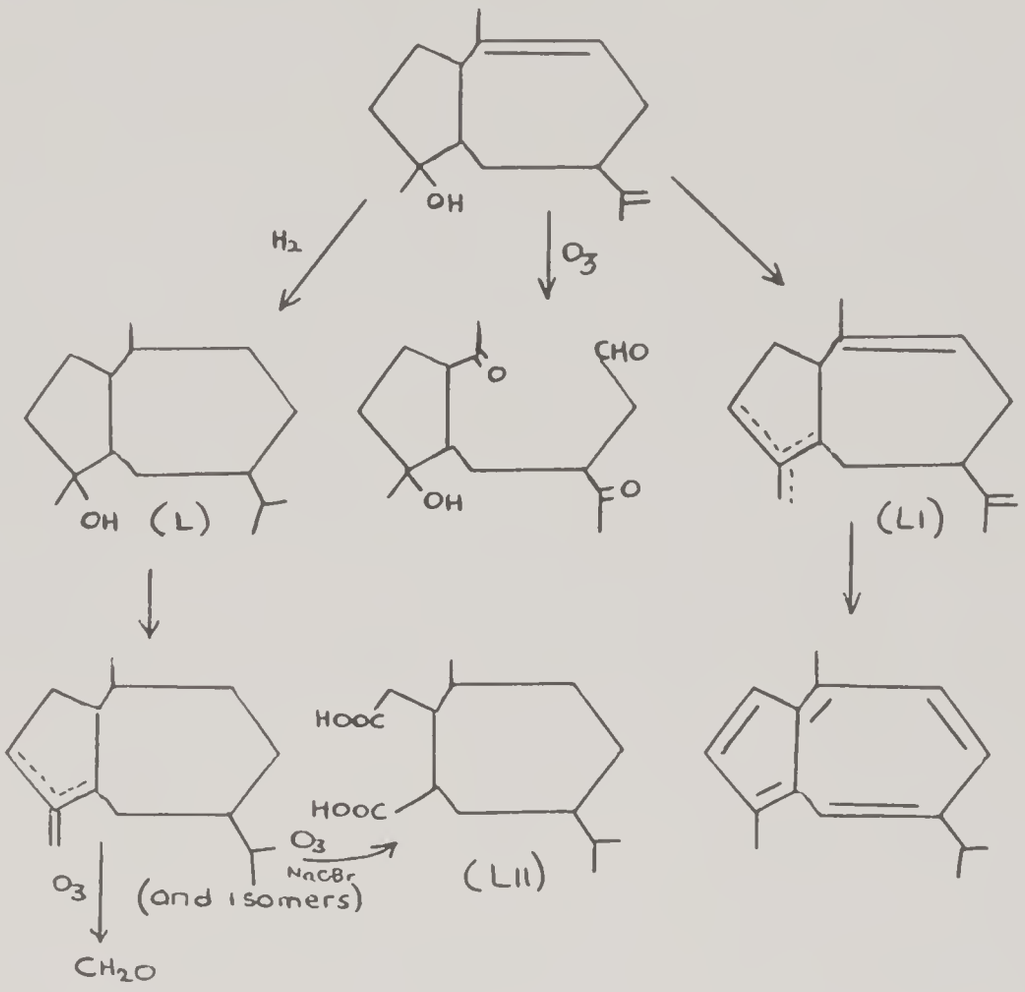


(XLVIII) (XLIX)

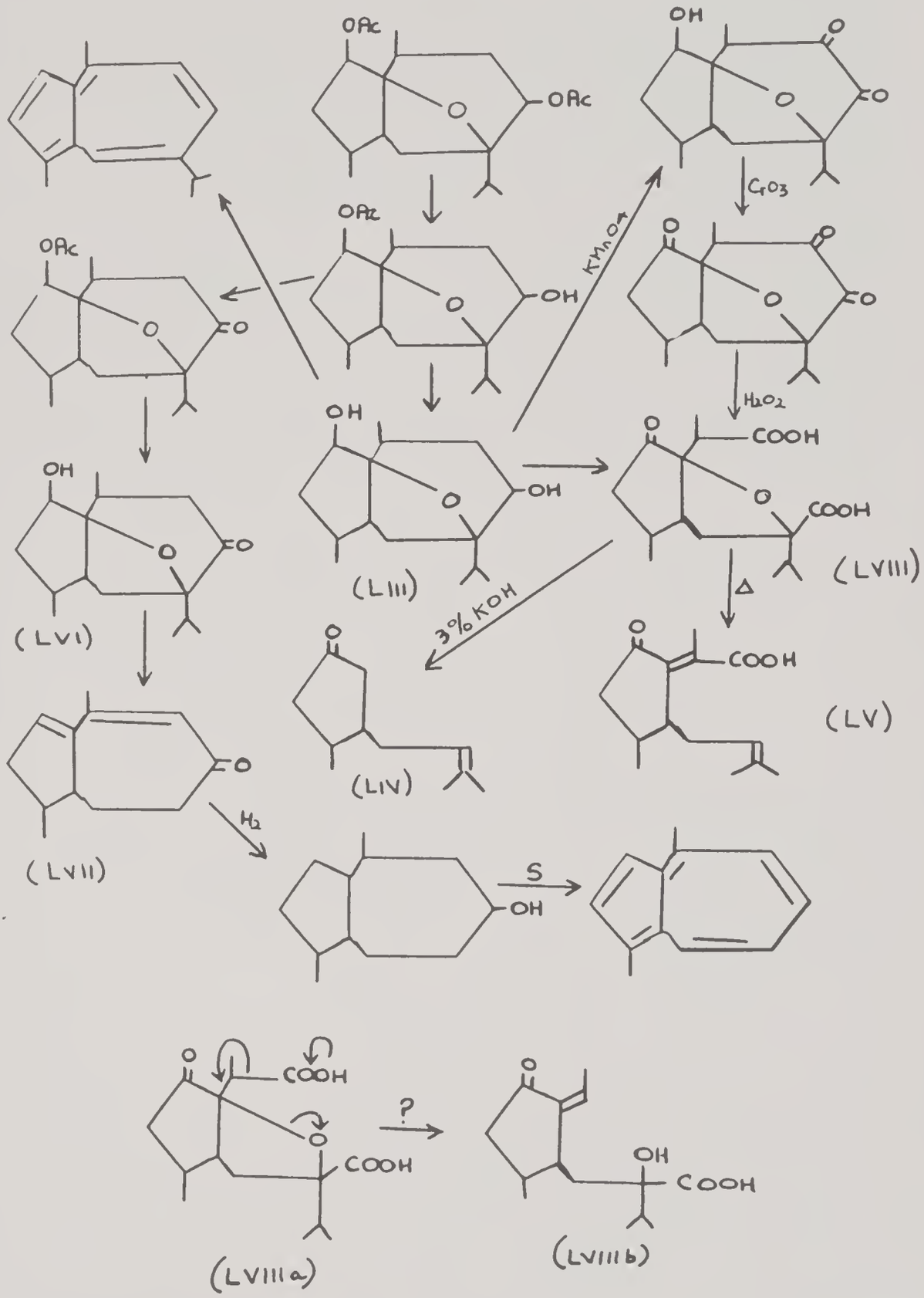
hypsochromic shift of the long wave bands was to be expected of an aldehyde in this position.

Partheniol is a tertiary alcohol which occurs as the cinnamate (13) in guayule (*Parthenium argentatum* Gray). It contains two double bonds, as shown by hydrogenation to a saturated tetrahydropartheniol (L). Dehydration with potassium bisulphate gave a mixture, anhydropartheniol (LI), which on dehydrogenation gave guaiazulene. The remaining features of the structure were elucidated by the standard transformations shown opposite, although the end products were not all well characterised. The dicarboxylic acid, an oil (LII), did *not* give a ketone on heating with acetic anhydride and was therefore presumed to be a glutaric acid.

Amongst the remaining sesquiterpenoids giving guaiazulene on dehydrogenation two of the most interesting are **kessoglycol** and the related **kessyl alcohol**, both of which occur naturally as acetates


OH
H_2
O_3
CHO
O
OH
O
OH (L)
(LI)
HOOC
HOOC
O_3
NaCBr
(LII)
O_3
(and isomers)
CH_2O

(14). The structure (LIII) is that proposed by Ukita. It is based mainly on the extensive reaction scheme shown opposite. The structures of the unsaturated ketone (LIV) and the keto acid (LV), together with (LVII), are firmly based on compelling degradative and synthetic work. A number of transformations are not mechanistically obvious in this scheme, and in particular those of (LVI) to (LVII) and of (LVIII) to (LV) and (LIV) may be cited. Thus, ethereal bridges (in formula LVI) are stable to base and the presence of the α-carbonyl group at one end does not facilitate its hydrolysis nor the loss of the attached *iso*propyl group. In (LVIII) thermal decomposition of the β-ethereal acid could lead to the presumably stable lactic acid derivative, i.e., (LVIIIa) $\rightarrow$ (LVIIIb), but not to (LV). Modification of (LIII) to (LIX) (15) allows of interpretation of these results. The conversion of (LVI) to (LVII) is then merely a β elimination followed by a dealdolisation represented by the

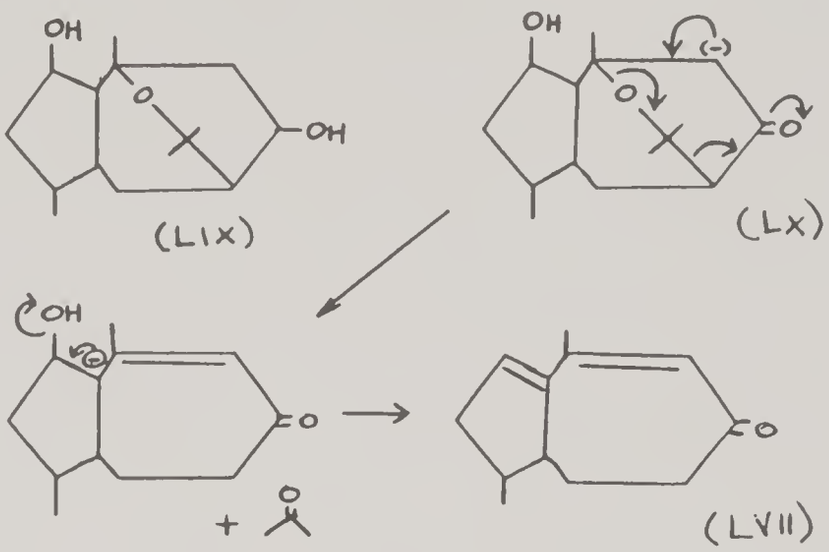

OAc
OAc
OH
O
CO
KMnO4
CrO3
H2O2
COOH
(LVI)
(LIII)
(LVIII)
3% KOH
Δ
(LIV)
(LV)
(LVII)
H2
S
?
(LVIIIa)
(LVIIIb)

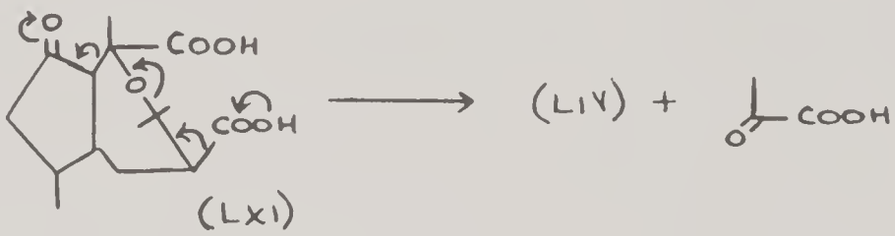
change (LX) to (LVII). The dicarboxylic acid (LVIII), now represented by (LXI), may then be considered to decarboxylate in base by a process resembling that of the base-catalysed decarboxylation of β-keto acids with the interposed oxygen atom playing the part of an electron bridge much as does an ethylenic linkage.

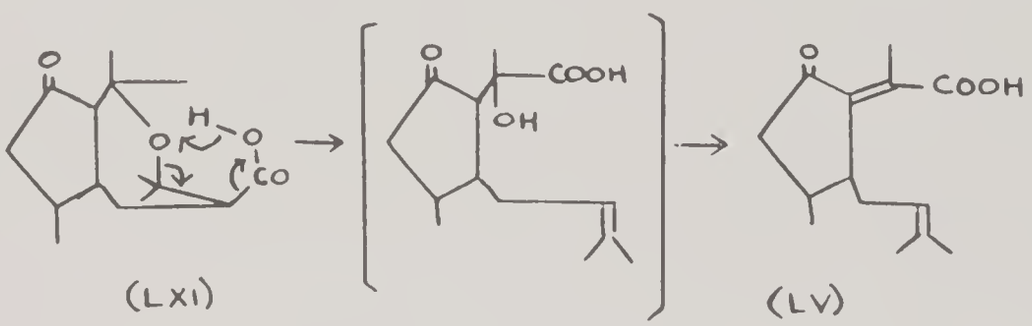
The thermal decomposition of (LXI) is that of a β-ethereal acid followed by a β elimination of water.

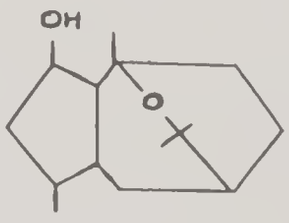
Since the relationship of kessoglycol to kessyl alcohol has been firmly established by the elegant work of Ukita (16), the formulation (LXII) for this latter substance appears in accord with present evidence.

Germacrol (17), linderene (18), α-chigadmarene (19), and the gurjunenes (20) are also guaiazulene derivatives. From linderene,


OH
OH
(LIX)
OH
O
O
(LX)
OH
O
+
O
(LVII)

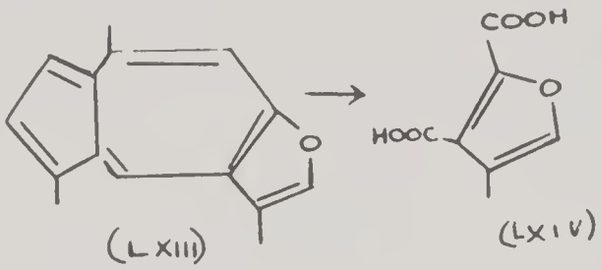

O
COOH
O
COOH
(LXI)
(LIV) +
COOH
O


O
H
O
O
CO
(LXI)
O
COOH
OH
O
COOH
(LV)

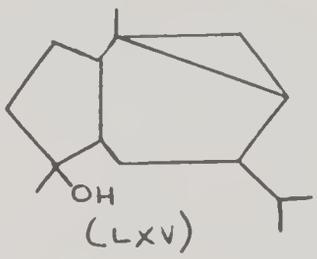

OH
O
(LXII)

by dehydrogenation, a new azulene, linderazulene (LXIII), has been obtained. Its structure has been proven by oxidation with hydrogen peroxide to (LXIV). (LXIII) has also been isolated by the dehydrogenation of a derivative of tenulin (page 268) and of matricin (page 26). **Ledol** (ledum camphor), isolated from Marsh tea oil, was formerly believed to be a cadalene derivative (LXVIa or LXVIb) (21). On the basis of oxidative degradations (22a) Kir'yalov has recently proposed the structure (LXV). If correct, this is surprising since some of the reactions, including dehydrogenation, must then involve non-Markownikoff cleavage of the *cyclo*propane ring. Nor does (LXV) readily account for the formation of cadalene, as well as guaiazulene, on dehydrogenation. Palustrol, isolated from the same source, is claimed to be the diastereoisomer of ledol (22b).

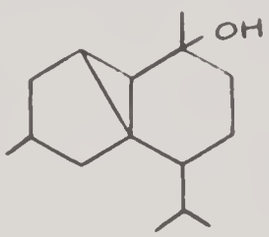
The oil of vetiver contains two isomeric unsaturated ketones, α- and β-vetivone. Their relationship to each other is not known, but they behave similarly chemically. **β-Vetivone** (LXVII) is an α:β-unsaturated ketone and is optically active, but by reduction with Raney nickel dihydro-β-vetivol (LXVIII) is obtained which is optically inactive; the molecule now has a plane of symmetry. Ozonolysis of β-vetivone gives acetone in good yield showing the presence of an *iso*propylidene group. Dehydrogenation gives vetivazulene (LXIX). Hydrogenation with platinum in acetic acid gives optically inactive tetrahydro-β-vetivol (LXX), and this may be oxidised by chromic acid to a racemic mixture of acids (LXXI). Ketonisation then gives (LXXII). Palladised charcoal dehydrogenation aromatised the six-membered ring to give (LXXIII) which has been identified by synthesis (23).



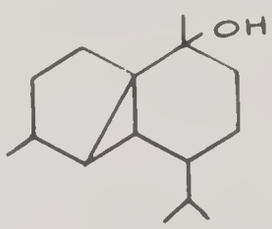
(LXIII) (LXIV)



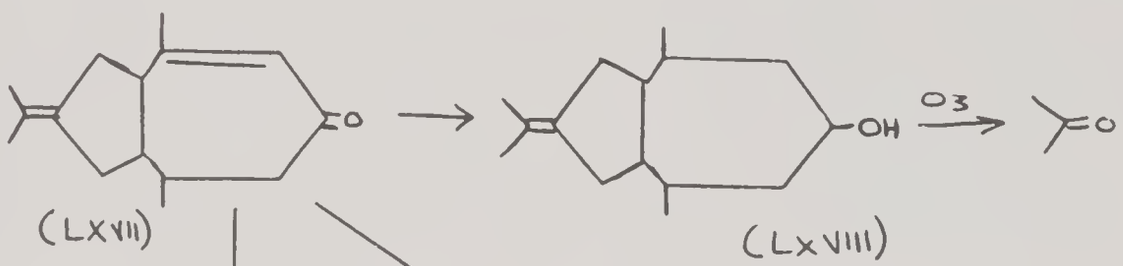
(LXV)



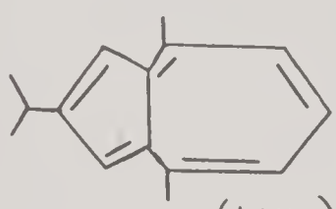
(LXVIb)



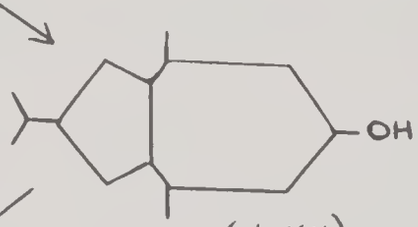
(LXVIa)



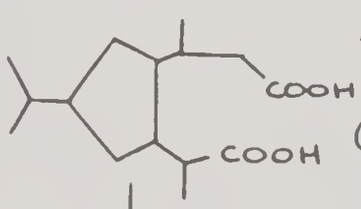
(LXVII) (LXVIII)



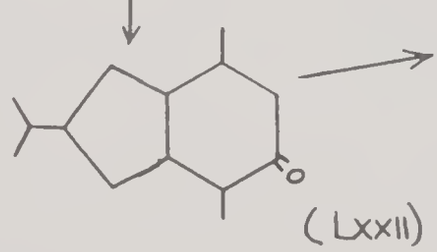
(LXIX)



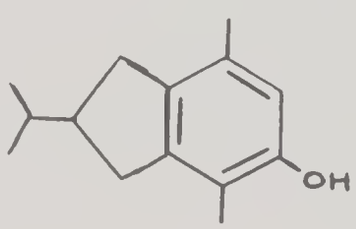
(LXX)



(LXXI)



(LXXII)



(LXXIII)

A hydrocarbon, tri*cyclo*vetivene (LXXIV), has been isolated very recently from the oil of vetiver (24). The infra-red spectrum (bands at 1640 and 890 cm^{-1}) indicated the presence of the grouping $CRR'{=}CH_2$, also confirmed by quantitative measurements for methyl groups in the infra-red (25). Oxidation of (LXXIV) gave the ketone (LXXV) which had a band, at 1718 cm^{-1}, in the infra-red, indicating that the carbonyl group was in a six-membered ring. Since vetivazulene was obtained on dehydrogenation, the structure (LXXIV) was proposed, supported by the reactions indicated opposite, and the implied relationship to the vetivones. Compounds (LXXVI) and (LXXVII) have a band at 1745 cm^{-1} in the infra-red, indicative of a *cyclo*pentanone, whilst the third ring in tri*cyclo*vetivene was isolated as 1:3-*cyclo*pentanedicarboxylic acid and identified by comparison with an authentic specimen.

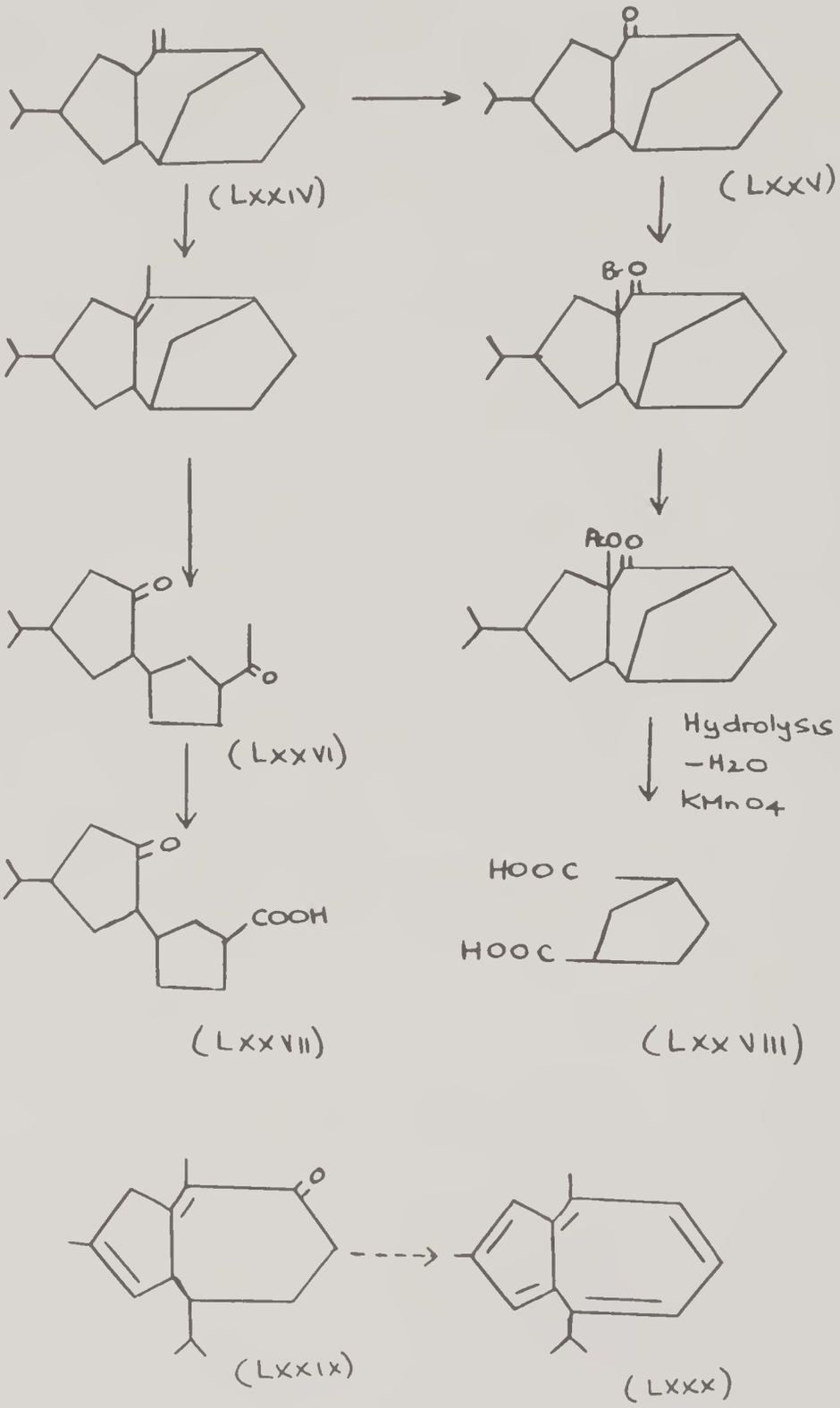
Zierone (LXXIX) (26) has been isolated from *Zieria macrophylla* Bonpland. Rigid evidence for the position of the isolated double bond has not been claimed, nor a distinction between positions 5 or 7 for the carbonyl group. On dehydrogenation of a derivative zierazulene (LXXX) is obtained, which is of particular interest in that it represents a new sesquiterpenoid skeleton; it has been synthesised.

THE LACTONIC AZULENE DERIVATIVES AND RELATED COMPOUNDS

This group may be divided into two sub-groups: (a) substances which appear to be extremely readily converted into chamazulene and (b) other compounds which do not have this property. The distinction may, however, be one of degree.

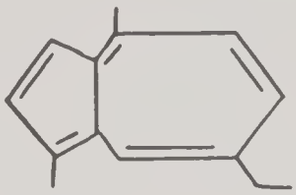
The Chamazulene Precursors

The blue azulene in oil of wormwood, was isolated by Sorm and his collaborators (27) and identified as chamazulene. During this work chromatographic separation was resorted to, and it was observed that preceding the dark blue azulene layer there was an orange band. This was a hydrocarbon which contained four ethylenic

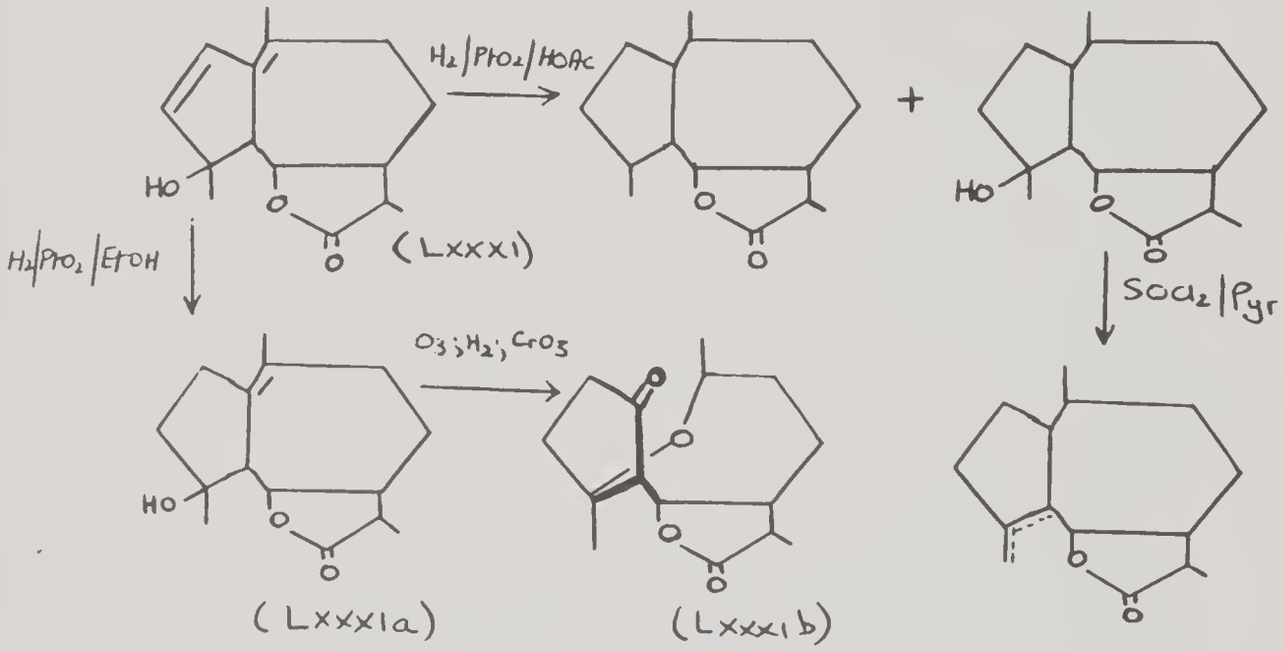

(LXXIV)
(LXXV)
(LXXVI)
(LXXVII)
(LXXVIII)
(LXXIX)
(LXXX)
COOH
HOOC
HOOC
Hydrolysis
$-H_2O$
$KMnO_4$

linkages only. In air it was unstable and was converted into chamazulene. It was therefore a dihydrochamazulene and was named chamazulenogen. From previous work chamazulene was known not to be present in another member of the *Compositae* family, *Matricaria chamomilla* or camomile, either as such or even as a hydrocarbon precursor, since in this case the precursor was readily extracted with water. The interest in chamazulene at this time was stimulated by medical investigation of its anti-inflammatory action, and the aqueous extracts of camomile were reported to possess a much greater anti-inflammatory action than could be explained by the presence of traces of chamazulene. It was assumed that in wormwood, similarly, a water-soluble chamazulene precursor must exist and after considerable difficulties the substance, a prochamazulenogen now named **artabsin** (LXXXI), was isolated. It was shown to be a hydroxy-γ-lactone containing two conjugated double bonds. On steam distillation this compound decomposed to give the orange chamazulenogen, and the process was facilitated by the presence of a small amount of an organic acid. The chamazulenogen itself in the presence of oxygen passes into chamazulene (27). On hydrogenation of artabsin (27b) in the presence of platinum oxide in acetic acid a mixture of saturated hydroxylactones and a saturated lactone (formed by hydrogenolysis) was obtained. One of the hydroxylactones was identical with that obtained from arborescin (page 274). The location of the hydroxyl group was restricted to positions 1 or 4 since dehydration gives a mixture containing some *exo*methylene compound, which, on ozonolysis, gives formaldehyde. Hydrogenation with ethanol as a solvent gives a substance with one double bond still present (LXXXIa). Ozonolysis of this (with reduction of the ozonide followed by mild oxidation) gives a ketone (LXXXIb) the carbonyl group of which has a band in the infra-red (at 1737 cm^{-1}) which indicates that it is in a five-membered ring. From this and other evidence the formula (LXXXI) has been proposed for artabsin. The structure of (LXXXIb) has not been rigidly established. The conversion to chamazulenogen is facile because allylic eliminations are involved.

The Czech workers then directed their investigations to oil of camomile and succeeded in isolating a crystalline chamazulene (as



CHAMAZULENE

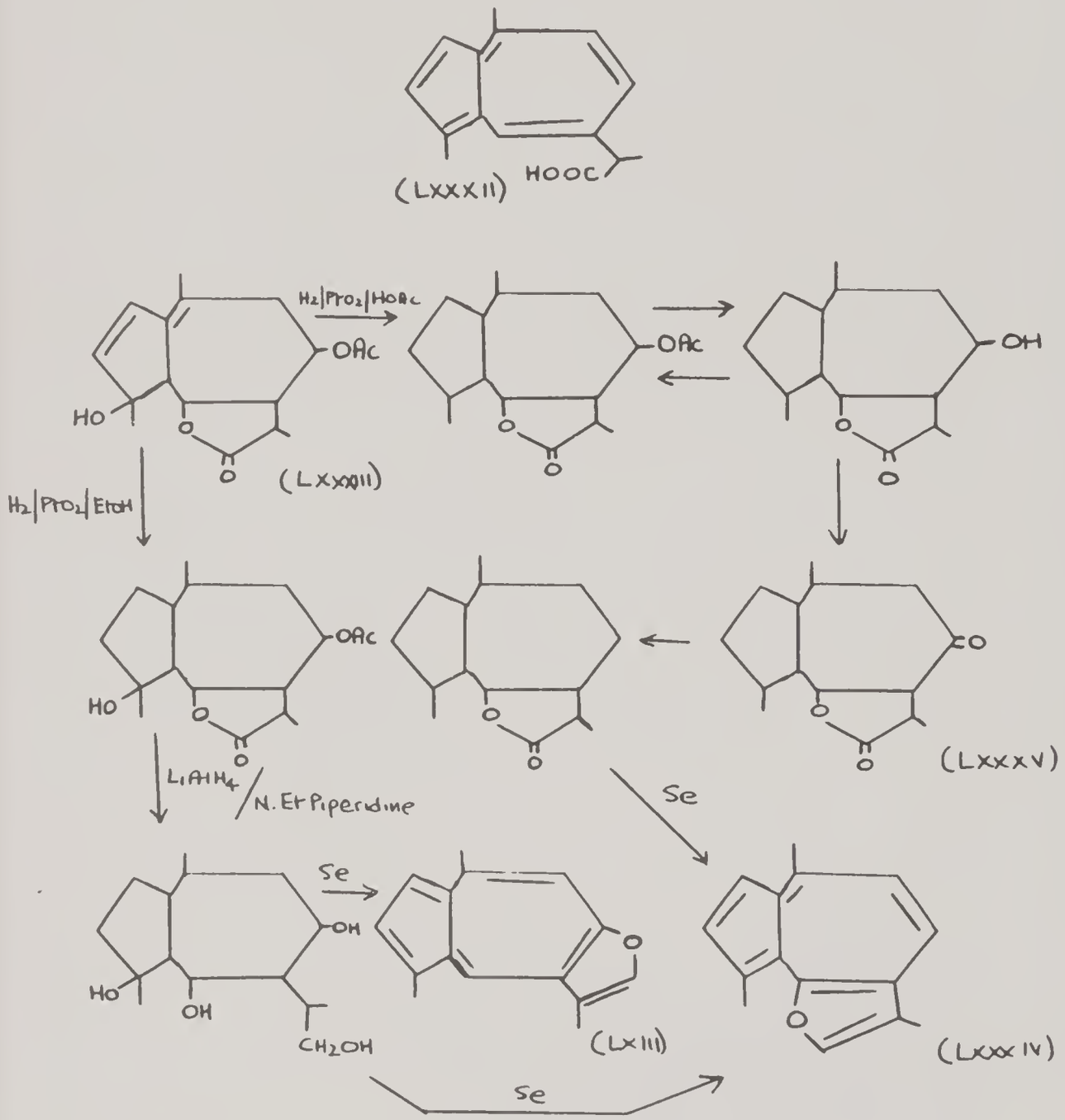


distinct from chamazulenogen) precursor, which differed from that in oil of wormwood in containing an additional acetoxyl group. This, by elimination, provided the extra double bond equivalent. In faintly acid solution decomposition began at about 50° and an intermediate acid was obtained as an oil. The spectrum of the ester resembled that of guaiazulene with a slight shift towards longer wavelengths. This acid, to which the formula (LXXXII) was ascribed, decomposed readily, giving off one molecule of carbon dioxide, to yield chamazulene. What is probably the same substance, **guaiazulenic acid**, has been isolated in cystalline form and investigated by Stahl (28) from yarrow (*Achillea millefolium* L.). This prochamazulene, **matricin** (LXXXIII), is therefore, another member of the guaianolide family. Hydrogenation of matricin (27b) with platinum oxide in acetic acid gives, with hydrogenolysis, a mixture of two stereoisomeric acetoxyguaianolides. By the steps shown this was converted through (LXXXV) to artemazulene (LXXXIV). Hydrogenation in ethanol did not result in hydrogenolysis and the product, which was stable to chromic acid, was converted stepwise into a mixture of artemazulene and linderazulene (LXIII) proving thereby the position of the acetate. The positioning of the hydroxyl group, which since it is stable to chromic acid must be tertiary, at C_1 is not rigidly proven, though it is rendered probable by cumulative negative evidence. It is not clear also why the ethanolic reduction in artabsin removes one double bond and in matricin two.

Recently, apart from prochamazulenogen, absinthine and anabsinthine have been isolated from wormwood and characterised; these substances are responsible for the bitter taste of wormwood. Although their structures have not been elucidated there is active work in this field (27c).

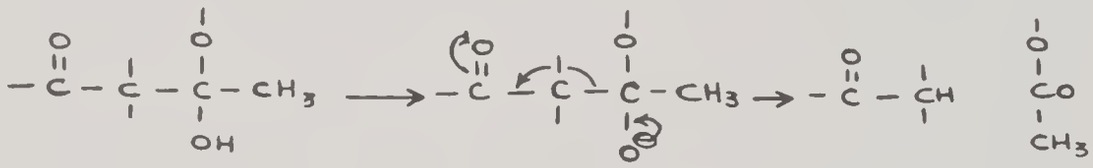
Perhydroazulene Lactones Not Readily Converted into Chamazulene

This group of substances, like the previous one, has only come to be investigated recently. **Tenulin** is the bitter principle found in various *Helenium* species. It was investigated by Clark and, later, mainly spectroscopically, by Ungnade (29). Later work has re-

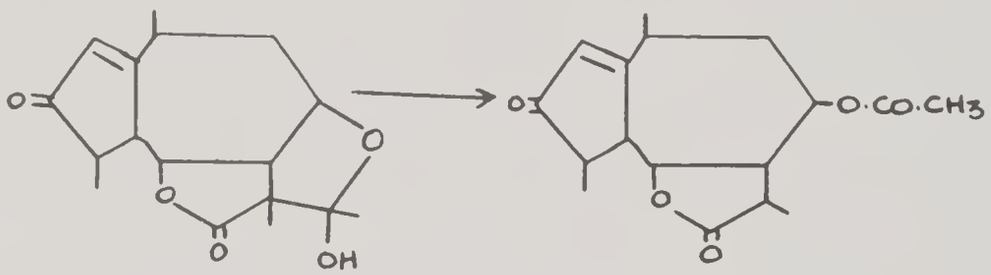

(LXXXII)
HOOC
H2|PtO2|HOAc
OAc
HO
(LXXXIII)
OAc
OH
H2|PtO2|EtOH
OAc
HO
CO
(LXXXV)
LiAlH4
N.Et Piperidine
Se
Se
OH
HO
OH
CH2OH
(LXIII)
(LXXXIV)
Se

sulted in structural proposals (30). Tenulin has the formula $C_{17}H_{22}O_5$ and on alkaline hydrolysis acetic acid can be obtained. It behaves chemically as a lactone and infra-red investigation also indicated the presence of a γ-lactone. The remaining oxygen atom is ketonic and forms part of an $\alpha:\beta$-unsaturated ketone. That the molecule was more complex than the above results would suggest was revealed by the facts that no bands characteristic of the acetate were visible in the infra-red and that acid hydrolysis under normal conditions did not give any acetic acid. On the other hand, its infra-red spectrum did suggest the presence of a hydroxyl group. These facts are rationalised in the acid-stable masked acetyl system (A). On treatment with base cleavage takes place to reveal a normal acetate (B), which may be hydrolysed in the ordinary way. This cleavage, a dealdolisation, does not take place under acid conditions unless they are very vigorous. The isomer (B), *iso*-tenulin, on reduction with potassium borohydride and dehydrogenation gave chamazulene, establishing the carbon skeleton, whilst reduction with lithium aluminium hydride and dehydrogenation gave linderazulene, providing confirmation. Since dihydrotenulin oxime underwent the same change, (A) to (B), a change that could be accomplished merely by boiling with hard water, the carbonyl group in (A) must be that of the lactone and not that of the unsaturated ketone. These transformations, on the basis of the structures finally deduced are as shown, where (LXXXVI) is tenulin and (LXXXVII) is *iso*tenulin. The carbonyl group was proven to be in a five-membered ring by, amongst other evidence, the presence in the infra-red of a band at 1738 cm^{-1} in dihydrotenulin (XC). Dihydrotenulin (XC) when refluxed with sodium acetate and acetic anhydride lost water to give anhydrodihydrotenulin (LXXXVIII), a vinyl ether which on ozonolysis gave a *bis*-α-lactone (LXXXIX). The relationship of the terminal of the ether, and hence of the acetate in *iso*tenulin relative to the γ-lactone, was therefore established. The dehydration of (XC) to (LXXXVIII) is facilitated by the ethereal oxygen atom.

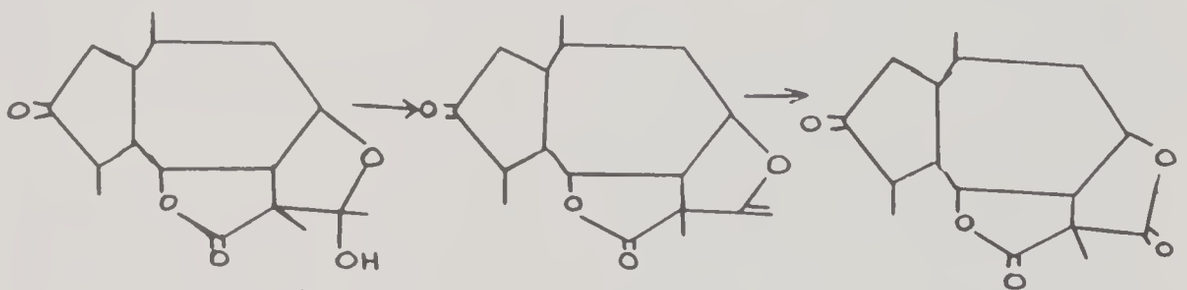
The position of the unsaturated ketone function in *iso*tenulin, and therefore in tenulin, could have been as in (XCI). This was



(A) (B)



(LXXXVI) (LXXXVII)



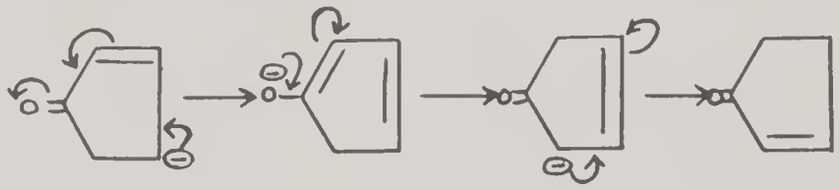
(XC) (LXXXVIII) (LXXXIX)

excluded in the following way. Treatment of (LXXXVII) with sodium hydrogen carbonate gave the alcohol derived from a new isomer, *neo*tenulin. This substance, also an $\alpha:\beta$-unsaturated ketone, was formed by the migration of the double bond around the five-membered ring as in (A $\longrightarrow$ B).

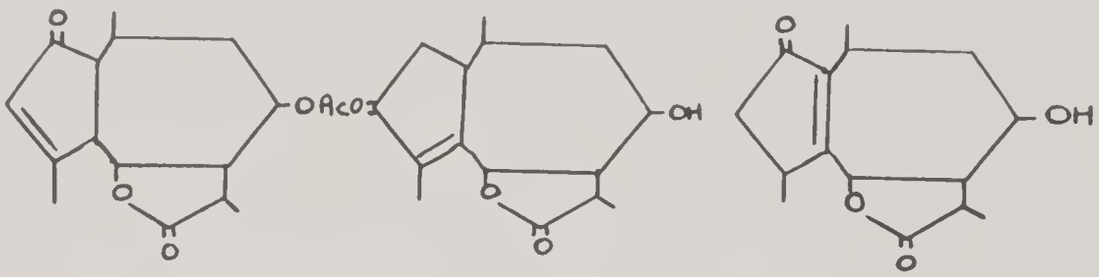
The position of the double bond in desacetyl*neo*tenulin (XCII) was shown by ozonolysis giving acetic acid, *not* obtained from (LXXXVII). The corresponding structure to be expected from (XCI) would be (XCIII) and this would give no volatile acid. (XCII) could be extracted directly from the bicarbonate solution, thereby showing that the lactone was still at its original position. This was placed as indicated in (XCII) by oxidation to the corresponding enedione. If the original substance had been the isomeric lactone (XCIV) the product would have been a *conjugated* enedione; both its ultraviolet and infra-red spectra were inconsistent with this. The double bond was not, for instance, reduced by zinc and acetic acid, and this is a property characteristic of ethylenic linkages between two carbonyl groups. All the features of the tenulin molecule apart from the stereochemistry are thus established. Very recently, confirmation as to the position of the lactone ring has been provided by Herz and his collaborators. They have prepared derivatives of tenulin in which the lactone function is said to be reversed, and have compared the properties of the diketones (XCV) and (XCVI). The former gives, apparently, a *bis*piperonylidene derivative.

Herz has made the interesting observation that dihydrodehydrodesacetyl*iso*tenulin is cleaved with alkali to give a dicarboxylic acid containing an $\alpha:\beta$-unsaturated ketone grouping. This may perhaps be better interpreted on the basis of (XCVI) rather than (XCV). The modified structure (XCVII) proposed by Herz does not explain the properties of *neo*tenulin (32).

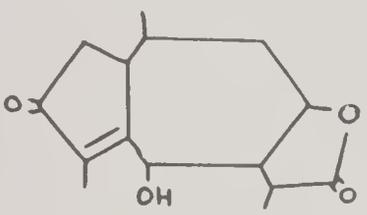
Helenalin is another bitter substance which is the active principle of sneezeweed, *Helenium microcephalum* L. It was investigated by Adams and Herz (33) in 1949 who showed that it was a *cyclo*pentenone, a α-lactone, and contained a secondary hydroxyl group. Evidence was also provided for an *exo* methylene group. An unidentified azulene was obtained on dehydrogenation. Reinvestigation recently by Büchi and Rosenthal (34) has provided the re-



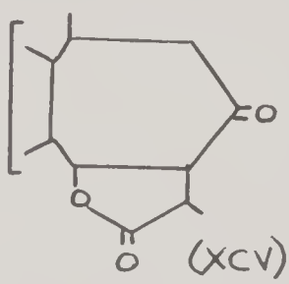
(A) (B)



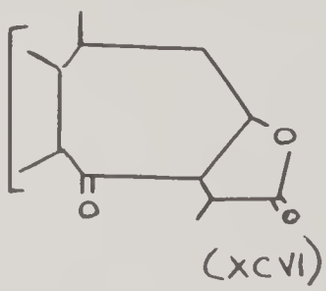
(XCI) (XCII) (XCIII)



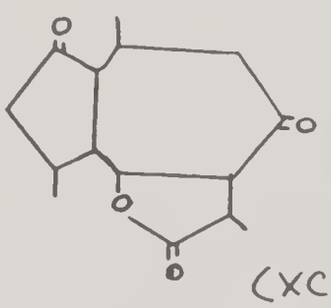
(XCIV)



(XCV)



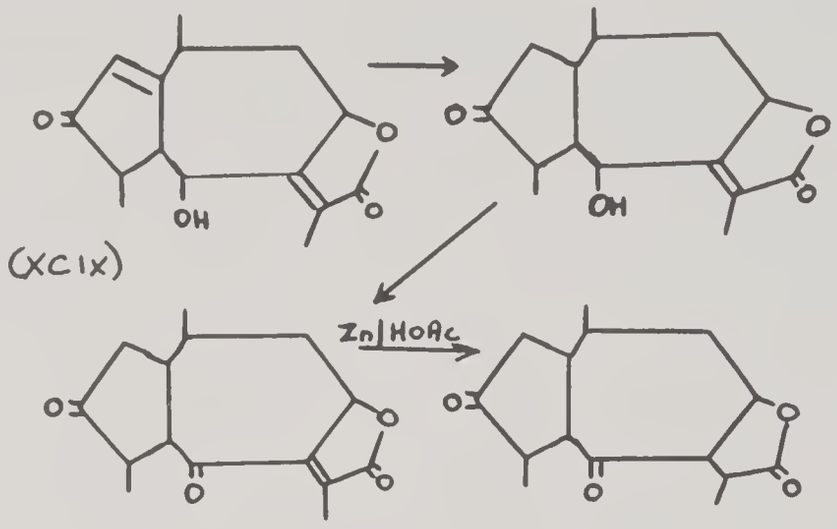
(XCVI)



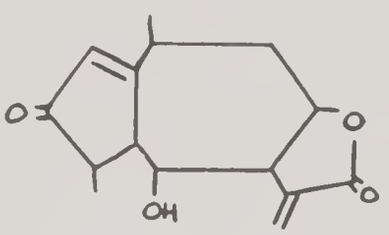
(XCVII)

maining required evidence. A study of the ultra-violet spectrum indicated that the methylene group was conjugated with the lactone. After hydrogenation to tetrahydrohelenalin (XCVIII) reduction and dehydrogenation gave guaiazulene. The position of the hydroxyl group was shown by the following series of reactions starting with an isomer of helenalin, *iso*helenalin (XCIX), found with helenalin in nature. The reduction of the double bond establishes the enedione system and the product (C), tetrahydrohelenalone, has also been obtained from helenalin. The structure (CI) was proposed for helenalin. The distinction between this and the structure (CIII) having the alternative unsaturated ketone environment was made by quantitative evaluations of the nuclear magnetic proton resonance spectra of helenalin and derivatives. The found proton signal ratios of $C{=}C-C-H$ to $C-H$ and CH_2 to CH_3 were close to those calculated. A similar process enabled a distinction between the two possible lactone positions to be made. Chemical confirmation would be desirable.

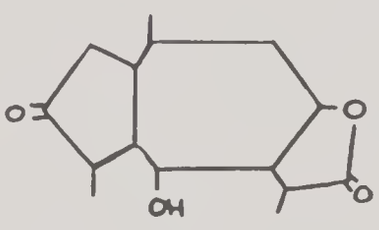
An isomer of artabsin has been isolated from *Artemisia arborescens* (38), and has been named **arborescine.** It contains a γ-lactone, a double bond, and an oxide bridge. This substance, which, unlike the chamazulene precursors, is not easily deoxygenated, by normal dehydrogenation methods gives chamazulene. Also, reduction of



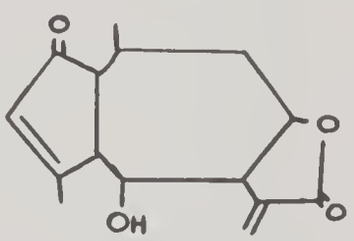
(XCIX) (C)



(CI)



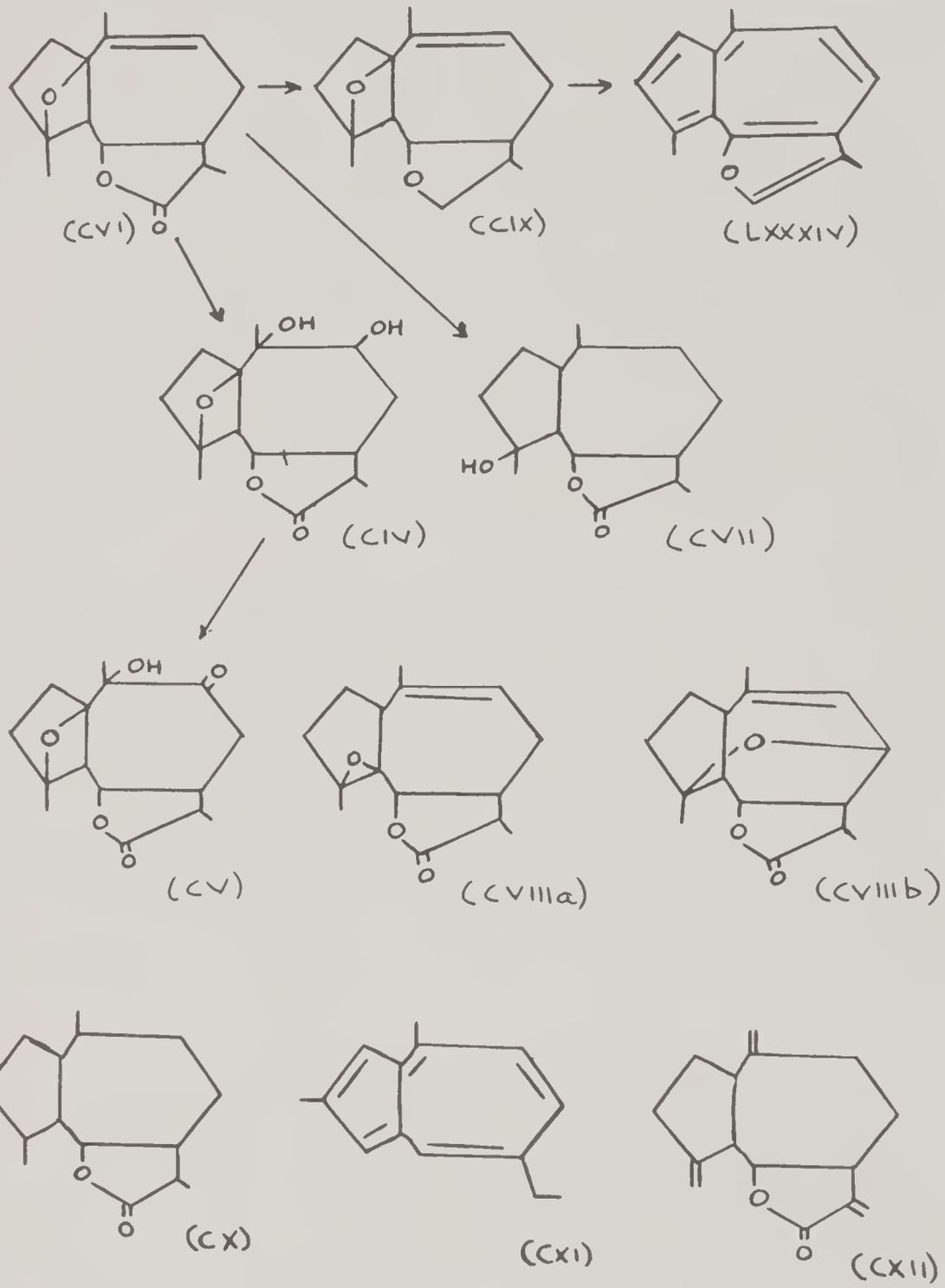
(XCVIII)



(CIII)

the lactone to the corresponding diol followed by treatment with *p*-toluenesulphonyl chloride gave a diether (CIX) dehydrogenated to give what is probably artemazulene (LXXXIV). The position of the double bond was shown as follows. Reaction with osmium tetroxide gave (CIV) oxidised to (CV) in which, since the carbonyl frequency of the ketone was 1710 cm^{-1}, required that it be placed in the seven-membered ring. Ozonolysis of arborescine afforded a keto acid which gave a positive iodoform test. Only the position 4 : 5 for the ethylenic linkage remained. The position of the oxide cannot be considered to have been rigidly established. One end is allylic to the double bond since hydrogenolysis gives a saturated tertiary alcohol (CVII), and the other was presumed tertiary because cleavage of the original ether gave a ditertiary glycol. The substance (CVII) has also been obtained by Sorm and his collaborators from artabsin (page 264). Allylic rearrangement during the acid-catalysed hydrolysis of the ether cannot, however, be excluded. Epoxide formulations such as (CVIIIa) were rejected because of non-reduction by lithium aluminium hydride and on the basis of this and other evidence the formula (CVI) was proposed. Even disregarding epoxide formulae a structure such as (CVIIIb) does not appear to be excluded. The trimethylene oxide bridge, if correct, is a feature so far unique in natural product chemistry.

The compounds **dihydrocostus lactone, costus lactone**, and **dehydrocostus lactone** occur in the higher boiling fraction obtained from the oil of costus (from the roots of *Saussurea lappa*. L). They are all bicyclic and contain one, two, and three ethylenic linkages, respectively. By hydrogenation of dehydrocostus lactone hexahydrocostus lactone was obtained (35) apparently identical with a compound of the same presumed structure (CX) obtained from carpesia lactone (page 276). By dehydrogenation a mixture of azulenes was obtained, elegantly resolved by paper chromatography, which included chamazulene and possibly Se-chamazulene (CXI). All three double bonds in dehydrocostus lactone were shown to be present in *exo* methylene groups by quantitative ozonolysis to give about three molecules of formaldehyde. This was confirmed by the infra-red spectrum which showed strong bands at 900 and 1647 cm^{-1} characteristic of the grouping $CRR' = CH_2$ and which showed no


(CVI)
(CIX)
(LXXXIV)
OH
OH
(CIV)
HO
(CVII)
OH
(CV)
(CVIIIa)
(CVIIIb)
(CX)
(CXI)
(CXII)

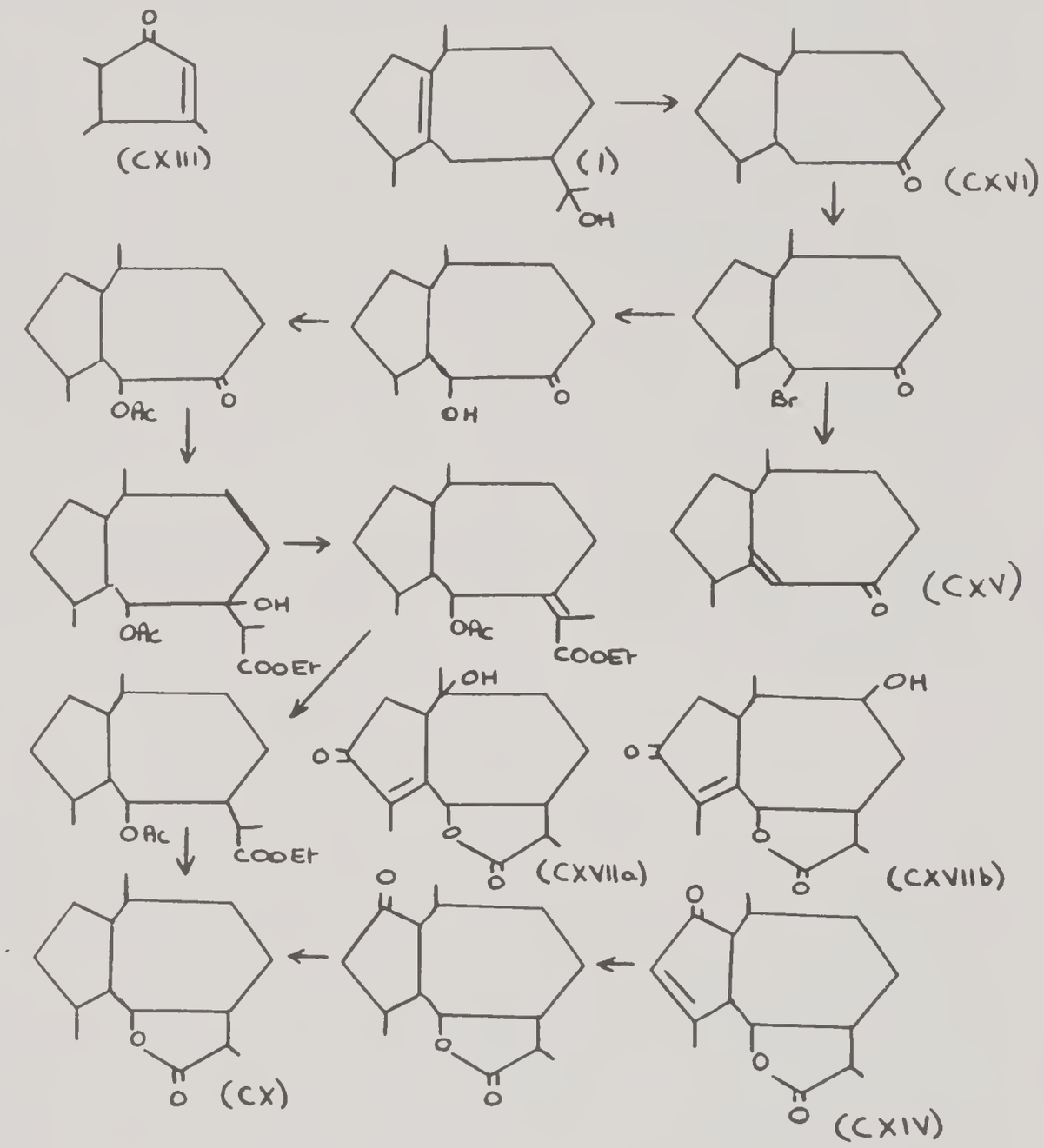
band at 1380 cm^{-1} where methyl groups would be expected to absorb. The structure (CXII) is that proposed.

Carpesia lactone is isolated from *Carpesium abrotanoides*. It is a liquid $\alpha:\beta$-unsaturated ketone. On hydrogenation (36) it affords a dihydro compound characterised as the 2:4-dinitrophenylhydrazone. No volatile aldehyde or ketone was obtained on ozonolysis, but the residue gave a positive iodoform test. The environment of the unsaturated ketone in (CXIV) was presumed to be as shown only by comparison of the spectrum with that of (CXIII). The structure (CXIV) was proposed, based essentially on the reactions shown opposite. The ketone (CXVI) was derived from guaiol (I) by hydrogenation and oxidation, and the position of the introduced substituent shown solely by the spectrum of the dehydrobrominated product (CXV).

Amongst the remaining substances which belong to this class may be mentioned **Geigerin** (37a) which contains an $\alpha:\beta$-unsaturated ketone and a hindered hydroxyl group. This substance which was isolated from "vermeerbos" (vomiting bush), represented by various species of *Geigera*, is believed to be related chemically to the poisonous active principle, vermeeric acid. The unsaturated ketone has been shown to be present in the five-membered ring, and on the basis of dehydrogenations and other evidence the formula (CXVIIa) has been proposed, identical (apart from stereochemistry) with that established for *iso*photosantonic acid lactone. Recent work (37b) has resulted in modification of the structure to, perhaps, (CXVIIb).

MISCELLANEOUS SESQUITERPENOIDS

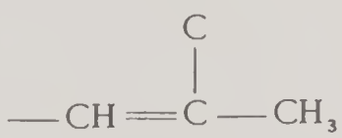
Most of the remaining sesquiterpenoids are substances showing far greater structural complexity than those so far mentioned. Their carbon skeletons are usually not easily classified by relation to simpler systems, such as azulene or naphthalene, and, as a consequence of their intricacy, dehydrogenation has often provided little evidence for their basic skeleton. Structural investigations have therefore had to resort to extensive degradation, often of a very laborious kind. In compensation, these compounds have a


(CXIII)
(I)
OH
(CXVI)
Br
OH
OAc
OAc
OH
COOEt
OAc
COOEt
(CXV)
OAc
COOEt
OH
(CXVIIa)
OH
(CXVIIb)
(CX)
(CXIV)

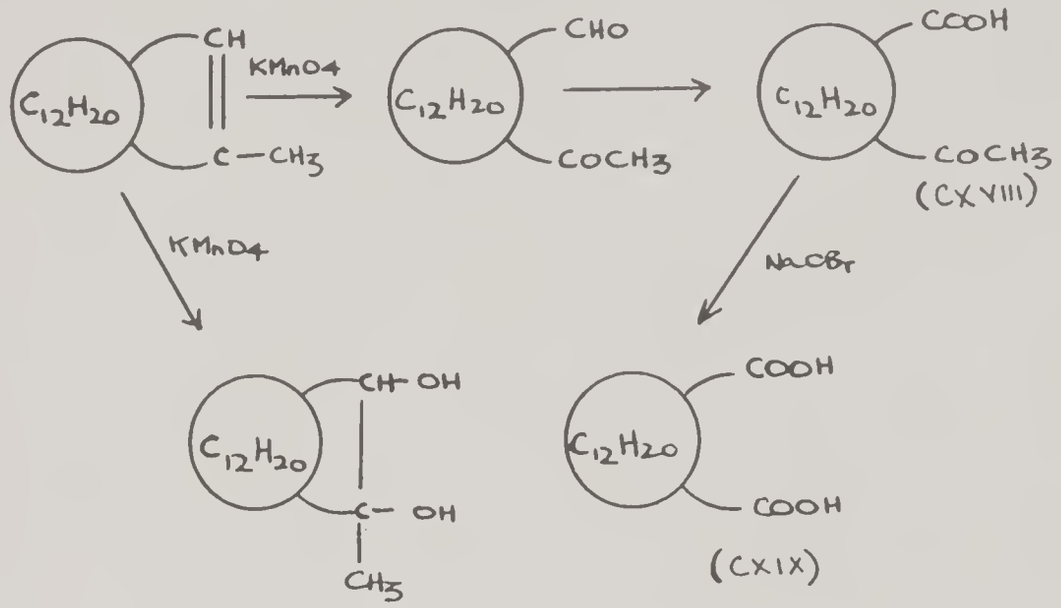
more varied and interesting chemistry than is found elsewhere in the simpler terpenoids. They will accordingly be dealt with in more detail.

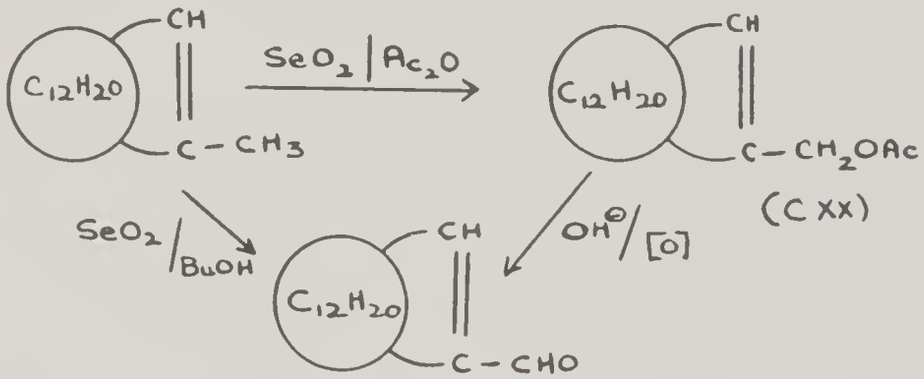
Cedrene

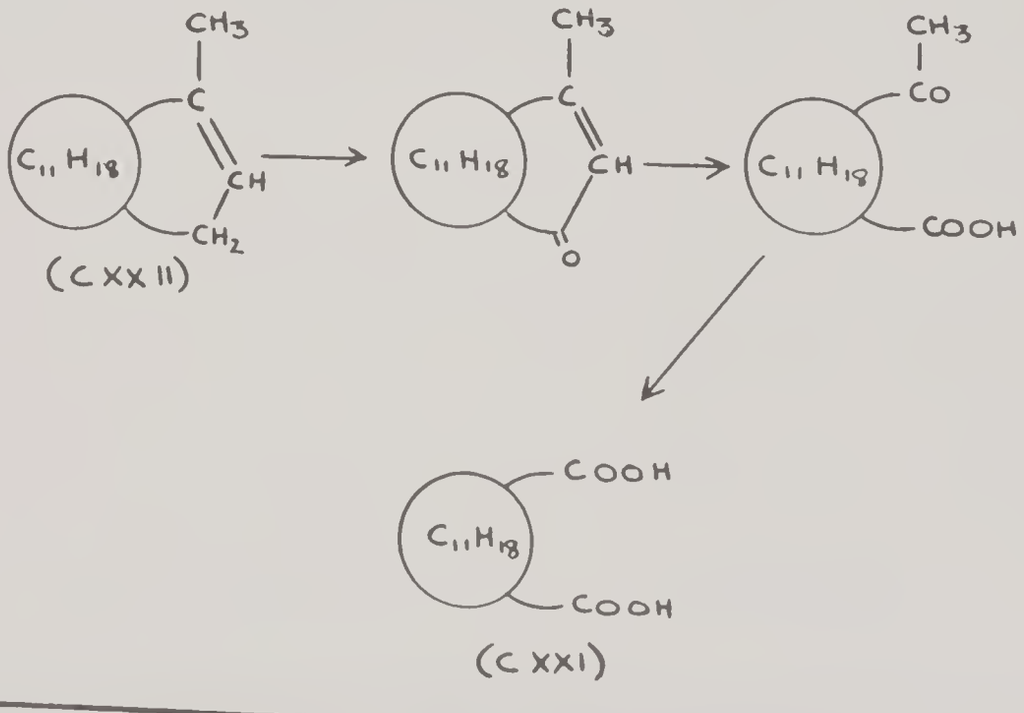
Cedrene is a hydrocarbon of the formula $C_{15}H_{24}$ which was first isolated by Walter, in 1841, from cedar wood oil. At the same time he isolated a crystalline alcohol, cedrol, also known as cedar or cypress camphor, which on dehydration gave cedrene. More recent work has shown that cedrene, as isolated from the oil, is a mixture of isomers. The main component, α-cedrene, is that obtained by the dehydration of cedrol, whilst another constituent, β-cedrene, contains an *exo*cyclic methylene group. Cedrol is a saturated tertiary alcohol. Cedrene therefore contains one double bond, and so from its empirical formula must be tricyclic. By oxidation with permanganate in acetone solution (39) three products are obtained, as shown opposite, and they establish the presence in cedrene of the grouping



The keto acid represented by the part formula (CXVIII) was oxidised by hypobromite to cedrenedicarboxylic acid (CXIX). This formulation was confirmed (40) by the oxidation experiment depicted below. The substance (CXX) is the acetate of an alcohol, primary cedrenol, which also occurs in the natural wood oil. Oxidation of α-cedrene with chromic acid gave an α:β-unsaturated ketone, cedrenone. Ozonolysis and further oxidation of the methyl ketone so produced gave another dicarboxylic acid, norcedrenedicarboxylic acid, represented by the partial formula (CXXI). This allowed the expansion of the partial formula of cedrene to (CXXII). The carboxyl groups of (CXXI) in contrast with those of (CXIX) are not similarly situated since the diester of (CXXI) was hydrolysed only as far as a monoester under conditions where the diester of (CXIX) was completely hydrolysed. In addition (CXIX) gave a di-


C12H20
CH
KMnO4
C–CH3
CHO
COCH3
COOH
COCH3
(CXVIII)
KMnO4
NaOBr
CH–OH
C–OH
CH3
COOH
COOH
(CXIX)

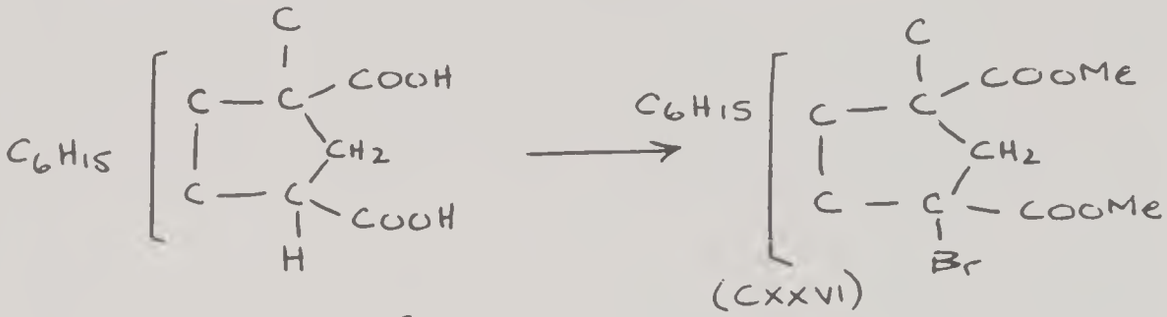

C12H20
CH
SeO2 | Ac2O
C–CH3
C–CH2OAc
(CXX)
SeO2 / BuOH
OH⊖ / [O]
C–CHO


CH3
C11H18
CH
CH2
(CXXII)
CO
COOH
O
COOH
(CXXI)

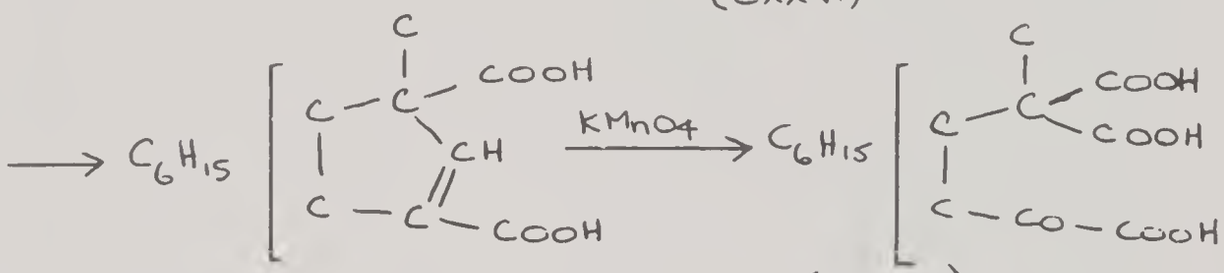
bromo compound, whereas (CXXI) gave only a monobromo derivative; one carboxyl of (CXXI) was therefore presumed tertiary.

The monobromo dimethyl ester (CXXVI) of (CXXI) on treatment with alkali (41) gave dehydronorcedrenedicarboxylic acid with the elimination of hydrogen bromide to give an $\alpha:\beta$-unsaturated acid; that no skeletal transformation had occurred was demonstrated by hydrogenation, with the absorption of one molecule of hydrogen, back to (CXXI). Oxidation of this acid with potassium permanganate afforded, after decarboxylation of an intermediate (not isolated) substituted malonic acid (CXXIII), a ketodicarboxylic acid (CXXIV), further oxidised by lead tetraacetate to a dicarboxylic acid anhydride (CXXV). These reactions, as later understood, may be represented by the partial formulae shown opposite. The presence of only one α-hydrogen atom in (CXXV) was confirmed by bromination to a monobromo derivative. The remaining carbon atoms contained the third ring of cedrene.

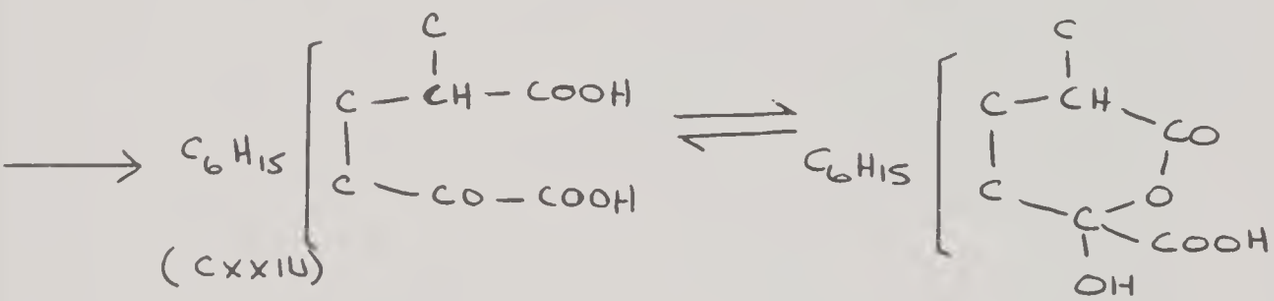
From these and other experiments a number of formulae for cedrene were deduced, but the problem was complicated, especially in the early stages, by the use of impure cedrene. Further, many people incorporated as a basis the supposed isolation of camphoronic acid (CXXVII) by the oxidation of cedrene with permanganate, followed by nitric acid. Reinvestigation showed that the compound was in reality $\alpha:\alpha$-dimethyltricarballylic acid (CXXVIII). In these earlier formulae the ring containing the ethylenic linkage was represented as five-membered, partly because cedrenedicarboxylic



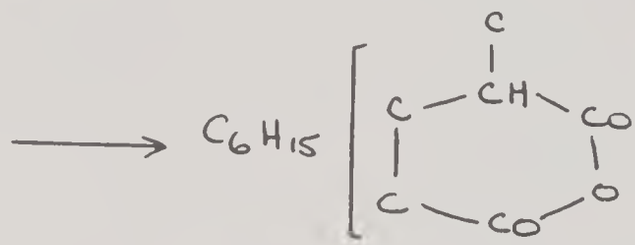
(CXXVI)



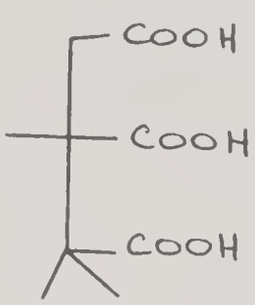
(CXXIII)



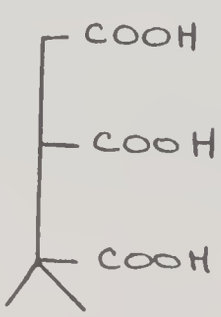
(CXXIV)



(CXXV)

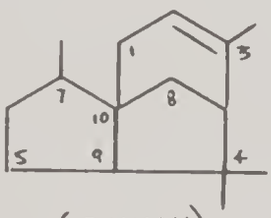


(CXXVII)

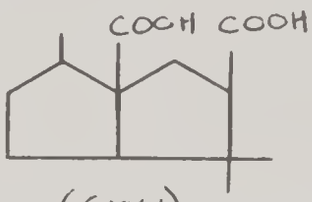


(CXXVIII)

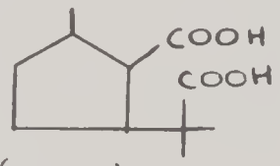
acid (CXIX) could not be cyclised to a ketone. The structure of cedrene was finally solved by two independent groups of workers in 1953. The American workers (42) showed that the anhydride of norcedrenedicarboxylic acid was a glutaric anhydride (bands in the infra-red at 1796 and 1765 cm^{-1}) and not a succinic anhydride (bands at 1852 and 1776 cm^{-1}) and that the ring containing the ethylenic linkage was therefore six-membered. The anhydride (CXXV) was also a glutaric anhydride, demonstrating that the second ring was five-membered. From these results and previous work, some of which has already been outlined, the structures (CXXIX), (CXXX), and (CXXXI) were proposed for cedrene, norcedrenedicarboxylic acid, and the dicarboxylic acid derived from (CXXV). The Swiss workers (43), in addition to similar spectroscopic evidence, showed that dehydrobromination of the bromo derivative (CXXXII) of (CXXXI) gave a dehydro derivative (CXXXIII) degraded, as shown, to (CXXXIV), which was identified by synthesis. The only alternative possible for the dehydro acid (CXXXIII) was (CXXXV), and this was rejected since the dehydro acid formed an anhydride; this, with (CXXXV), would have been a contravention of Bredt's rule. Since (CXXXI) formed an anhydride the carboxyl and dimethyl acetic residues were *cis*. Hydrogenation of (CXXXIII) gave an isomer of (CXXXI) which was also *cis*, and therefore differed in the configuration of the methyl group. Assuming catalytic *cis* addition of hydrogen the second isomer must be represented by (CXXXVI) and so the original stereochemistry was (CXXXVII) and so, in cedrene, the methyl group and the hydrogen atom at C_9 are on the same side of the molecule. The configuration at C_{10} is not meaningful as regards the stereochemistry of cedrene itself since it was involved in the decarboxylation of the malonic acid (CXXIII). Two possibilities then remained depending on whether the two five-membered rings were fused *cis* or *trans*. The solution



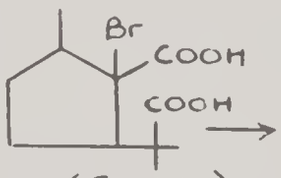
(CXXIX)



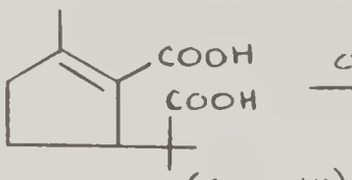
(CXXX)



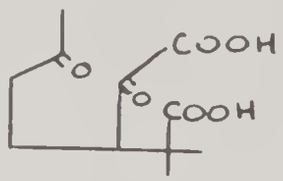
(CXXXI)

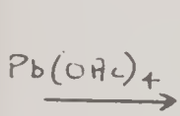


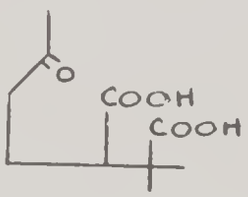
(CXXXII)

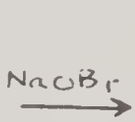


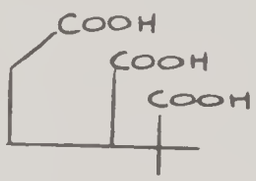
(CXXXIII)



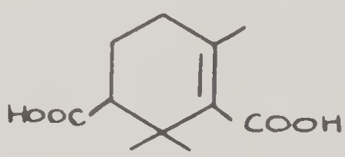




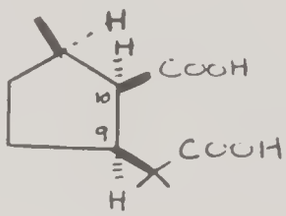




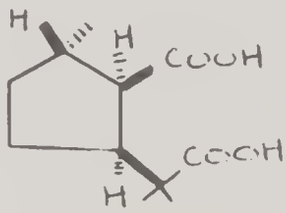
(CXXXIV)



(CXXXV)



(CXXXVI)

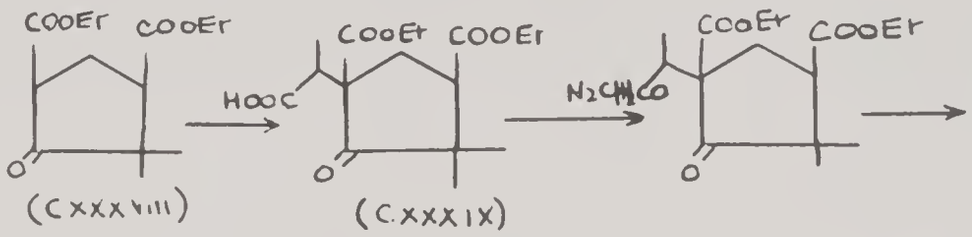


(CXXXVII)

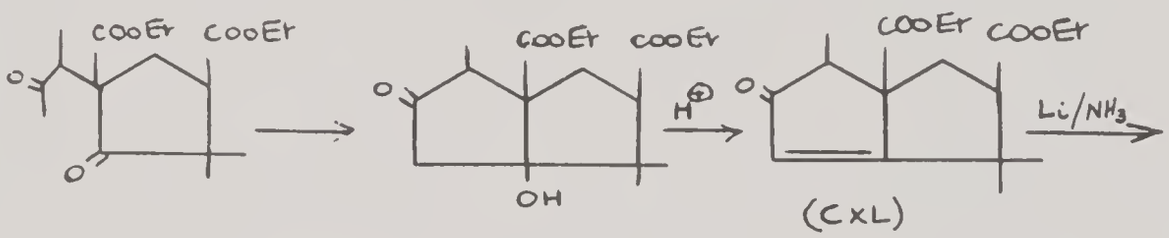
to this was forthcoming in the total synthesis of cedrol by Stork and Clarke (44).

The starting material was the *cyclo*pentanone (CXXXVIII) previously obtained by Simonsen (45). Alkylation with benzyl-α-bromopropionate and hydrogenolysis gave (CXXXIX) converted, into (CXL) by the steps shown. Reduction with lithium in liquid ammonia gave the far more stable *cis* fusion of the two five-membered rings. The methyl group was in its more stable configuration as shown by its non-epimerisation with alkali. Removal of the ketone and hydrolysis then gave norcedrenedicarboxylic acid which was resolved with quinine. The monoester was converted through the acid chloride into the methyl ketone (CXLI), then base-cyclised to (CXLII). Lithium aluminium hydride reduction gave a mixture of alcohols which was oxidised with chromic acid and catalytically reduced to (CXLIII); reaction with lithium methyl then gave cedrol (CXLIV).

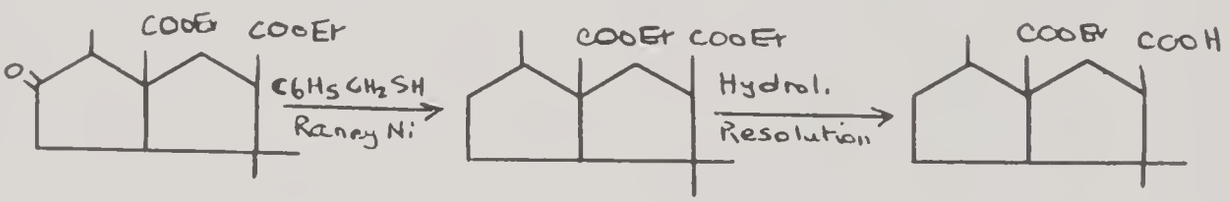
An interesting transformation in cedrene chemistry is the production of the bromodicarboxylic acid from the (CXXVI). This is, in terms of the final structure of cedrene, (CXLV). Although the ester gives as main product the simple dehydrobrominated derivative, the acid when so treated undergoes simultaneous decarboxylation, and the product (CXLVI) is *not* an α:β-unsaturated acid. This reaction has been rationalised as being essentially a *neo*pentyl solvolysis, the mechanism being as represented. This reaction is analogous to the conversion of α-bromocamphoric anhydride to laurolenic acid already described (page 140). (CXLVI) was also obtained from (CXLI) by treatment with peracid to give the acetate, hydrolysis and reaction with phosphorus tribromide, solvolysis and

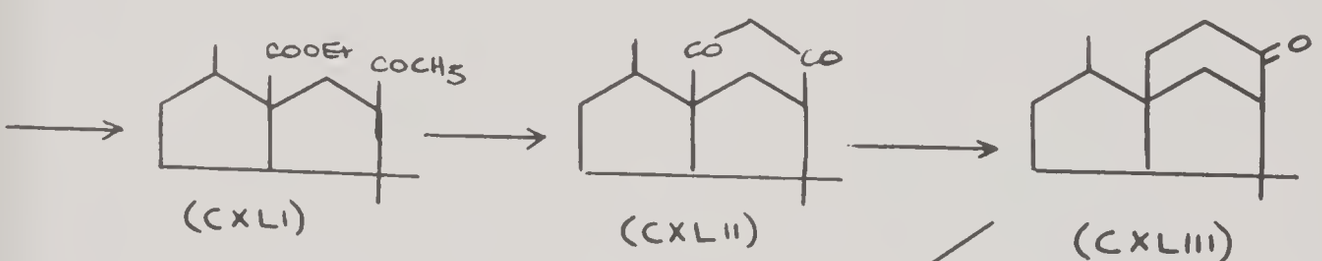


(CXXXVIII) (CXXXIX)

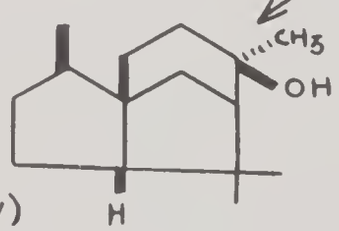


(CXL)

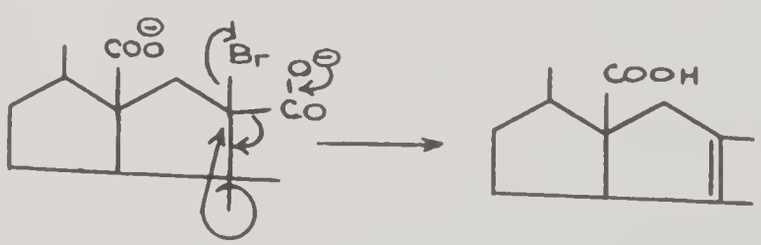




(CXLI) (CXLII) (CXLIII)



(CXLIV)



(CXLV) (CXLVI)

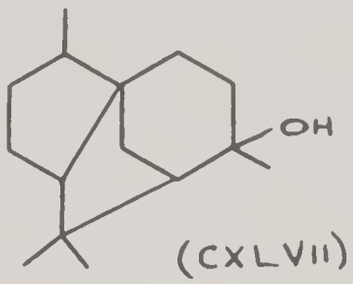
rearrangement. The relationship of cedrol to the cadalene group of sesquiterpenoids can more clearly be seen from the expression (CXLVII).

Caryophyllene

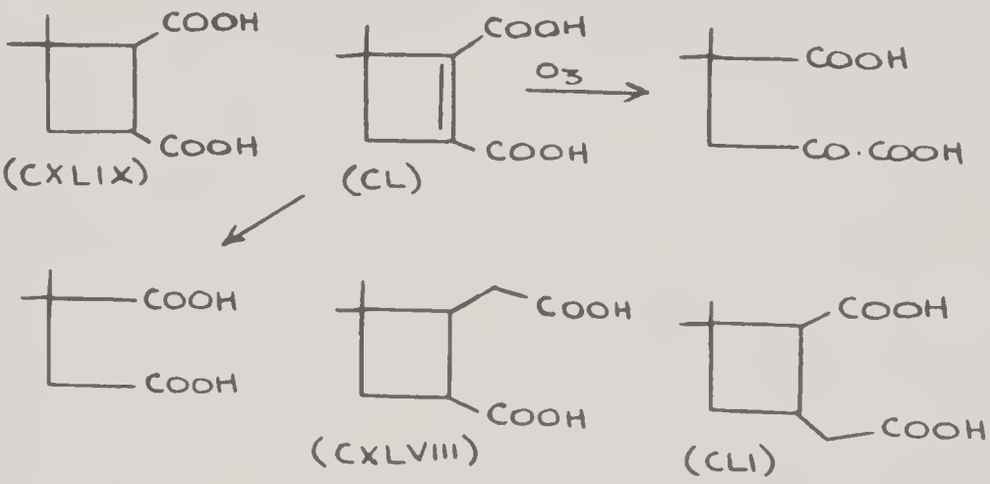
From oil of cloves (from *Eugenia caryophyllata*) a sesquiterpenoid hydrocarbon mixture has been obtained which is the main source of the compound caryophyllene. In the older literature the terms α-, β-, and γ- have been applied to substances from this source. α-Caryophyllene is now recognised as being humulene, whilst γ-caryophyllene is, in fact, an artefact. These prefixes have now been discarded and the term caryophyllene is used without further specification.

Caryophyllene is one of the most remarkable and versatile of terpenoids of any class in its variety of skeletal transformations. Whilst the study of this terpenoid dates from about 1875 it is only very recently that the nature of its subtle rearrangements has been discovered and understood.

Caryophyllene has the formula $C_{15}H_{24}$ and since there are chemical indications of two double bonds it must be, therefore, bicyclic. The nature of one of these rings was established at an early date by oxidative degradation. Ozonolysis of caryophyllene gives as one product a ketocarboxylic acid of the formula $C_{11}H_{18}O_3$. On oxidation further with nitric acid a mixture of two dicarboxylic acids was obtained, one of which, caryophyllenic acid (CXLVIII), is the homologue of the other, named norcaryophyllenic acid (CXLIX). The latter compound was shown to be a *cyclo*butane derivative by bromination and dehydrobromination to give (CL) further degraded as shown. This was confirmed later, in 1936 (46), by the synthesis of (+)-*trans*-2-carboxy-3 : 3-dimethyl*cyclo*butanecarboxylic acid identical with (+)-norcaryophyllenic acid. Of the alternatives, (CXLVIII) and (CLI), for caryophyllenic acid, decision in favour of (CXLVIII), as predicted by Barton (47), was obtained firstly by the synthesis of (CLI), the incorrect isomer, and subsequently by the total synthesis and resolution of (CXLVIII) (48). Oxidation of the keto acid, $C_{11}H_{18}O_3$, with hypobromite gave the next higher homologue of caryophyllenic acid, homocaryophyllenic acid (CLII), and the structure of this was again demonstrated by homologation from (CXLVIII).

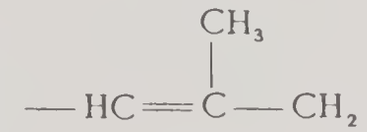


(CXLVII)



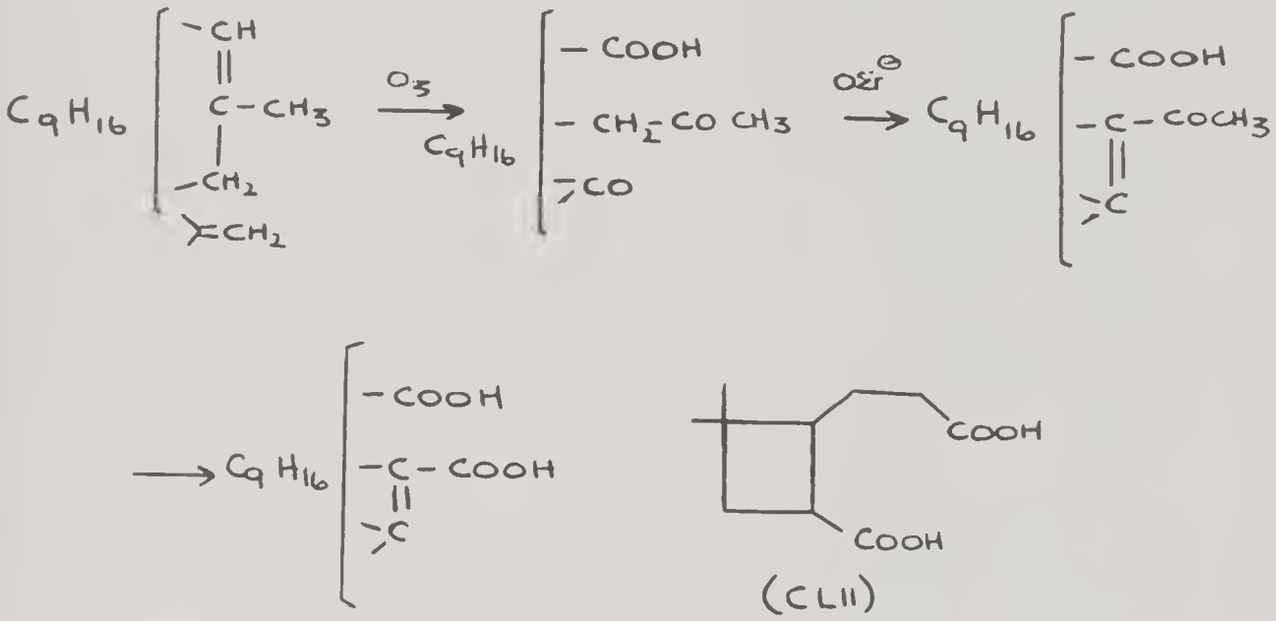
(CXLIX) (CL) (CXLVIII) (CLI)

One of the double bonds in caryophyllene must be situated in an *exo* methylene group since various oxidative experiments, and in particular ozonolysis, had shown formaldehyde could be obtained. The second must be contained in the system



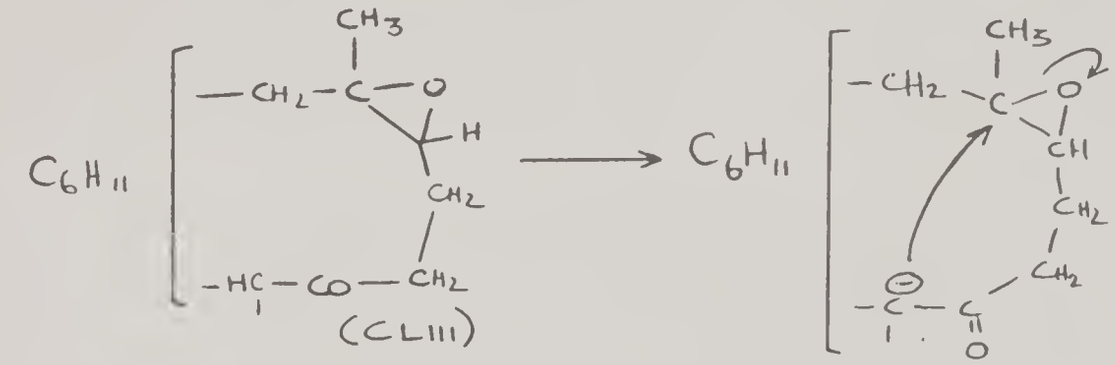
The evidence for this is contained in the sequence of partial formulae (49) shown opposite. Since (CLII) had been obtained by oxidation the second ring in caryophyllene contained at least six carbon atoms. Evidence that it contained a far larger ring was obtained in the following way. Treatment of caryophyllene with hydrogen peroxide gave a crystalline monoepoxide which could be oxidised, with removal of the *exo* methylene carbon atom, to an oxido ketone containing fourteen carbon atoms. By a study of the infra-red carbonyl frequencies of this and related substances (50), Sorm and his collaborators were led to propose a nine-membered ring as constituting part of the caryophyllene framework. The structures proposed for caryophyllene were, however, incorrect.

Independently other workers (51) had arrived at similar conclusions as regards the presence of a nine-membered ring. This was achieved by establishing the relationship, in the molecule, of the

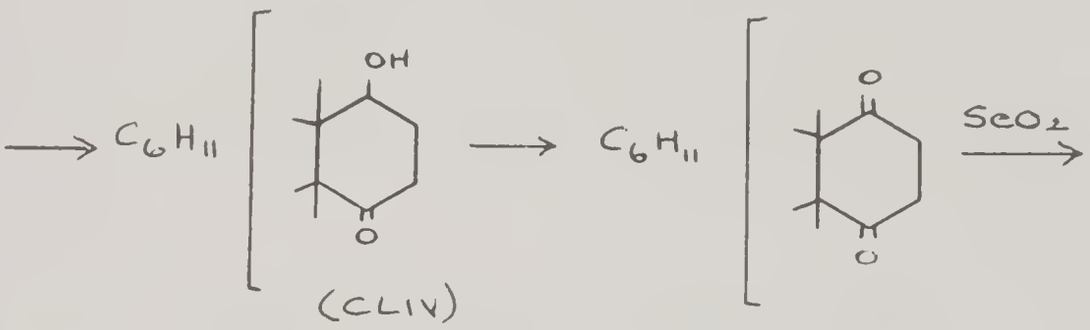


(CLII)

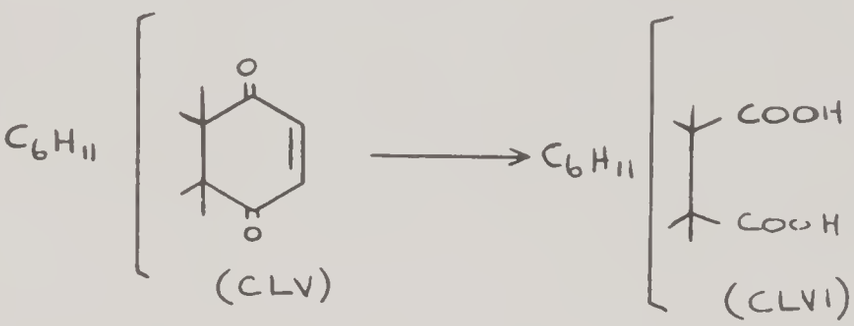
two double bonds. By treatment of the oxido ketone (CLIII) with base, cyclisation was induced, to give a tricyclic hydroxy ketone (CLIV). This was then degraded by successive oxidation with chromic acid and selenium dioxide to the ene-1 : 4-dione (CLV) recognised by its characteristic spectral properties ($\lambda_{max.}$ 221 mμ), and by its further oxidation to a saturated bicyclic dicarboxylic acid (CLVI) that readily formed an anhydride suggesting a substituted succinic anhydride. In the partial formulae shown opposite the six-carbon fragment contained the dimethyl*cyclo*butane moiety. These and other results could be accommodated only in the formulae (CLVII), (CLVIII), and (CLIX) of which (CLVII) and (CLVIII) were those originally favoured by the Czech workers. At this point Ramage and his collaborators (52) demonstrated that homocaryophyllenic acid and the methyl ketone from which it was derived were genuine caryophyllene transformation products, as might not have been the case starting with a liquid hydrocarbon, by making use of a blue crystalline nitrosite obtainable from caryophyllene by the action of nitrous fumes. Direct oxidation of this with potassium permanganate led to the $C_{11}H_{18}O_3$ ketocarboxylic acid. The presence of two methylene groups between the *cyclo*butane ring fusion and the methyl group was, therefore, required. Formulae (CLVII) and (CLVIII) could therefore be excluded. At the same



(CLIII)

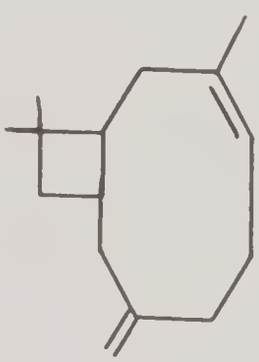


(CLIV)

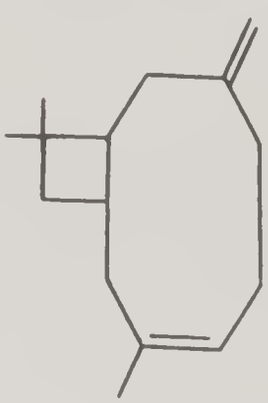


(CLV)

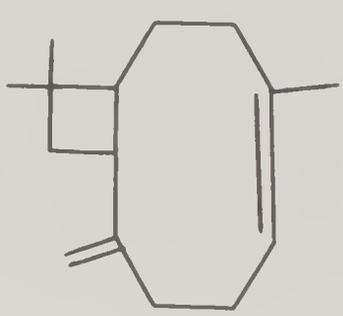
(CLVI)



(CLVII)



(CLVIII)



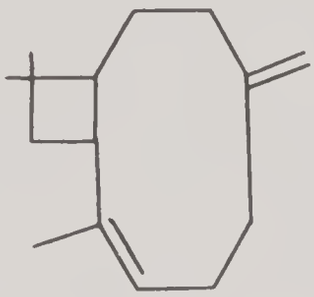
(CLIX)

time these workers proposed the alternative (CLX) as the structure of caryophyllene. The dicarboxylic acid (CLVI) derived from the two formulations (CLX) and (CLIX) would be (CLXI) and (CLXII), respectively.

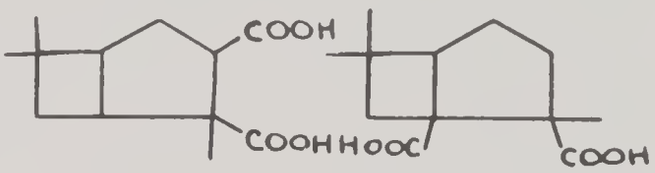
Barton and his collaborators (53) adduced evidence to demonstrate that the dicarboxylic acid was ditertiary (as in CLXII) and not secondary-tertiary (as in CLXI): it could not, for instance, be brominated. It should be noted that in any case a certain mobility of the ethylenic linkages would be required in (CLX) to fit the available chemical evidence. The compelling evidence provided by Barton in favour of (CLIX) was supported by the degradation shown opposite carried out by Atwater and Reid (54) on dihydrocaryophyllene (CLXIII). Such a degradation based on (CLX) is not possible.

The existence of an isomer of caryophyllene in clove oil has been the subject of debate for some time. It has now been shown that *iso*caryophyllene is a genuine entity and that it differs from caryophyllene in having the more stable *cis* configuration about the double bond. The conversion from the unstable to the stable isomer takes place by the action of nitrous acid (as in making the nitrosite) or during catalytic reduction (Pd) of the *exo* methylene group to dihydrocaryophyllene (55)—which is in fact dihydro*iso*caryophyllene. The assignments were made, in the first place, on the rates of reaction of the two isomers with per acid, it having been previously established by Prelog (56) that *trans-cyclo*nonene, being more strained, is more reactive than the *cis* isomer. The assignments so made were subsequently confirmed by a study of the tricyclic derivatives of caryophyllene.

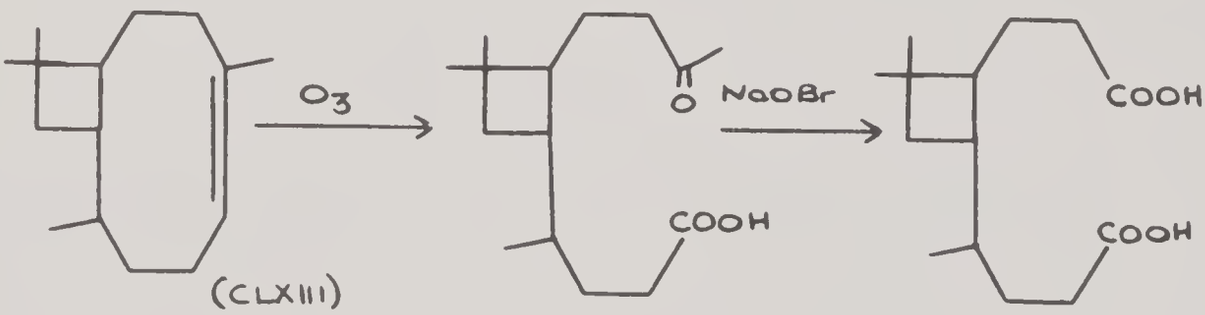
Carophyllene, by the action of a number of acidic reagents may be cyclised to give a substance originally known as β-caryophyllene alcohol, but now termed caryolan-1-ol, together with a hydrocarbon, clovene. On the basis of an extensive degradative scheme



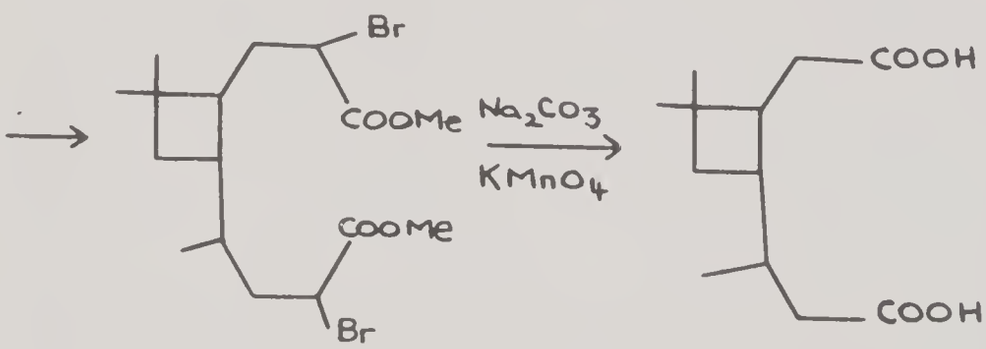
(CLX)



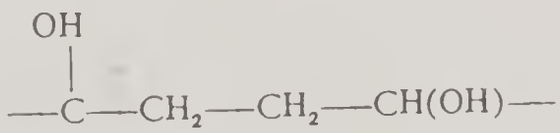
(CLXI) (CLXII)



(CLXIII)

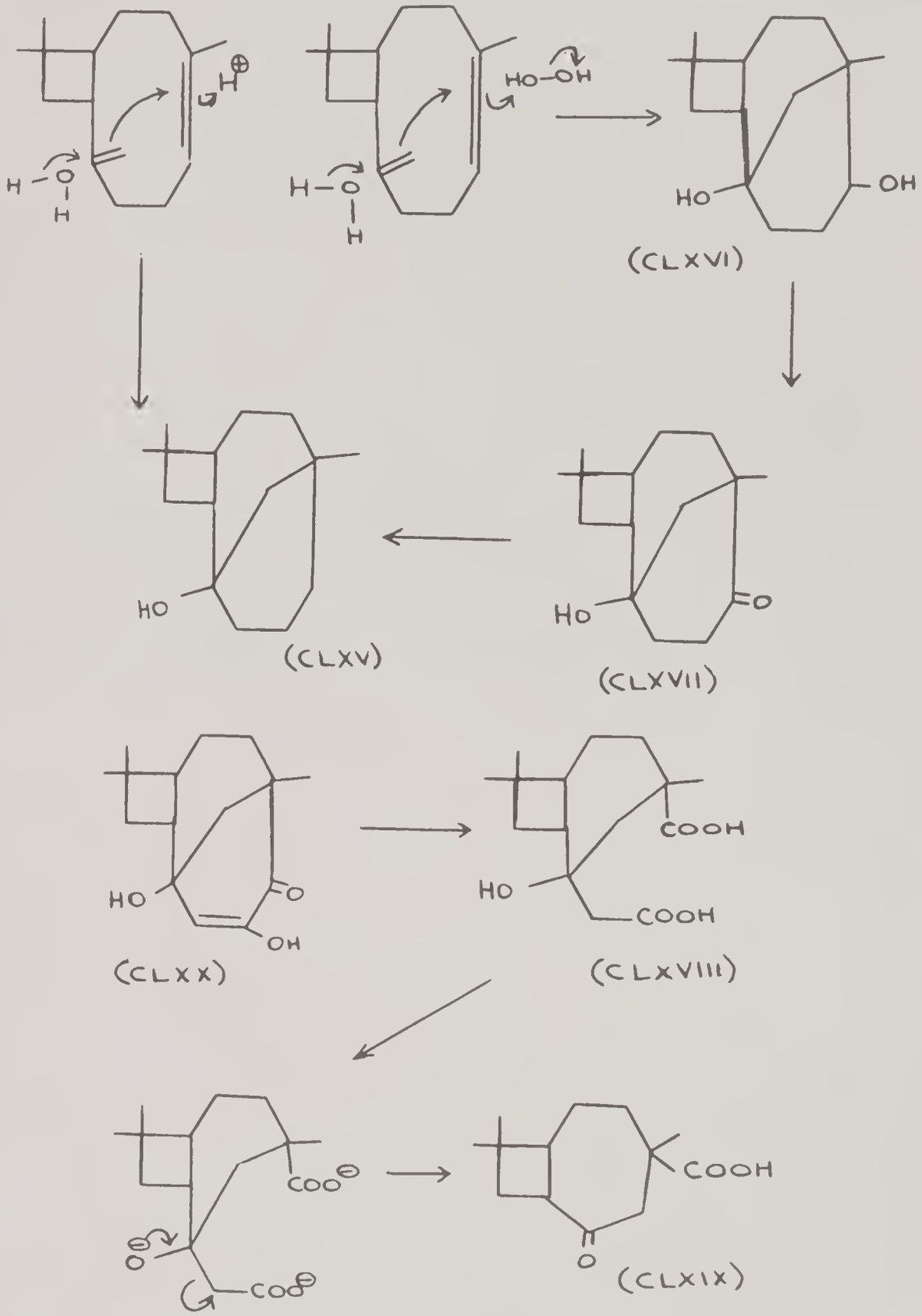


Barton and his collaborators have ascribed the structure (CLXV) to the former substance. A by-product, obtained in the epoxidation of caryophyllene, has been shown to have the same skeleton as caryolanol by the reactions shown opposite. Its genesis, by the action of hydrogen peroxide, is believed to parallel that of caryolanol by the action of acid. Oxidation of (CLXVII) with selenium dioxide gave the enolised α-diketone (CLXX) (diosphenol) ($\lambda_{max.}$ 276 mμ) which was cleaved by hydrogen peroxide to the dicarboxylic acid (CLXVIII). This could be dehydrated with phosphorus oxychloride in pyridine and when ozonised gave the keto acid (CLXIX). A simpler process was merely to heat (CLXVIII) with strong base when, as shown, acetic acid would be eliminated by dealdolisation. These reactions proved the presence in (CLXVI) of the grouping



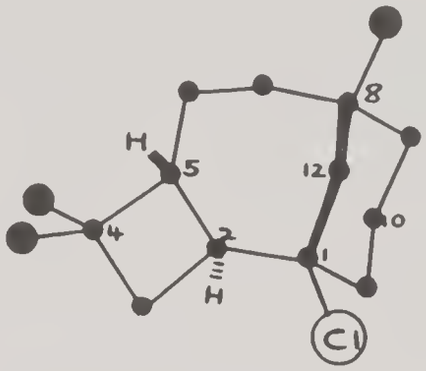
The structure of (CLXIX) was confirmed by demonstration (a) of the presence α to the carbonyl group of an enolisable centre, and (b) that the carboxyl group was very hindered. Caryolanol, by the action of phosphorus pentachloride, is converted to the corresponding chloride. This reaction, and the conversion of the chloride to the acetate by the action of sodium acetate in acetic acid, are of theoretical interest because they represent substitution at a bridgehead, where inversion of configurations is impossible, and an intermediate carbonium ion may be hypothesised (73). The reaction takes place because the rings are large enough in a 4 : 3 : 1 system such as in caryolanol to permit a considerable degree of planarity in the ion.

The structure of caryolanyl chloride was conclusively established by the brilliant X-ray investigation of Robertson and Todd (57). Their analyses also established the *trans* fusion of the two rings in caryolanyl halides and therefore in caryophyllene itself and have

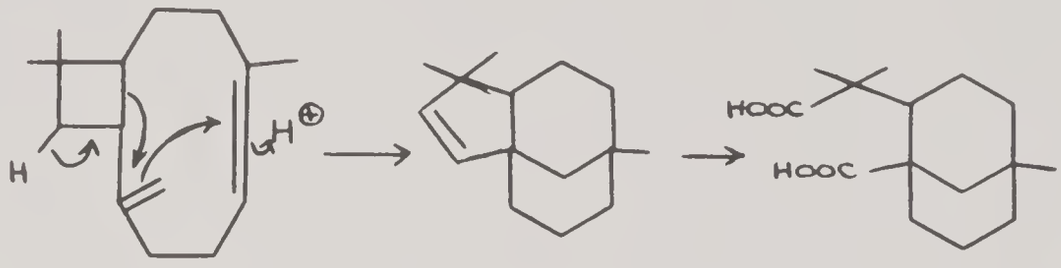

HO
OH
(CLXVI)
HO
(CLXV)
HO
O
(CLXVII)
HO
O
OH
(CLXX)
HO
COOH
COOH
(CLXVIII)
COO⊖
COOH
O
(CLXIX)

shown that the hydrogen atom at C_5 lies on the same side of the molecule as does the methylene bridge as indicated in (CLXXI).

The hydrocarbon clovene (CLXXII) a by-product in the acid cyclisation of caryophyllene has yet a different carbon skeleton. It is tricyclic and contains an ethylenic linkage: oxidative cleavage of the double bond gives a ditertiary dicarboxylic acid, clovenic acid (CLXXIII). The formation of clovene might be envisaged, as shown in (CLXXIV), as further reaction of the carbonium ion formed at C_1 (with bond migration and loss of a proton) in the absence of a nucleophile to saturate the reaction centre as occurs in the formation of caryolanol. The ion at C_1 cannot lose a proton from an adjacent carbon atom since this would result in the formation of a double bond at a bridgehead. Although this may not be an explicit contravention of Bredt's rule, which applies to smaller ring fusions, such a feature would involve considerable strain. A 1:2 shift is therefore the result. The preference for one bond rather than the other to migrate is presumably geometrical. It should, however, be mentioned that caryolanol is not itself an intermediate since under similar acid conditions to those leading to clovene it is unaffected whilst with more vigorous treatment a hydrocarbon, *iso*clovene, is formed.



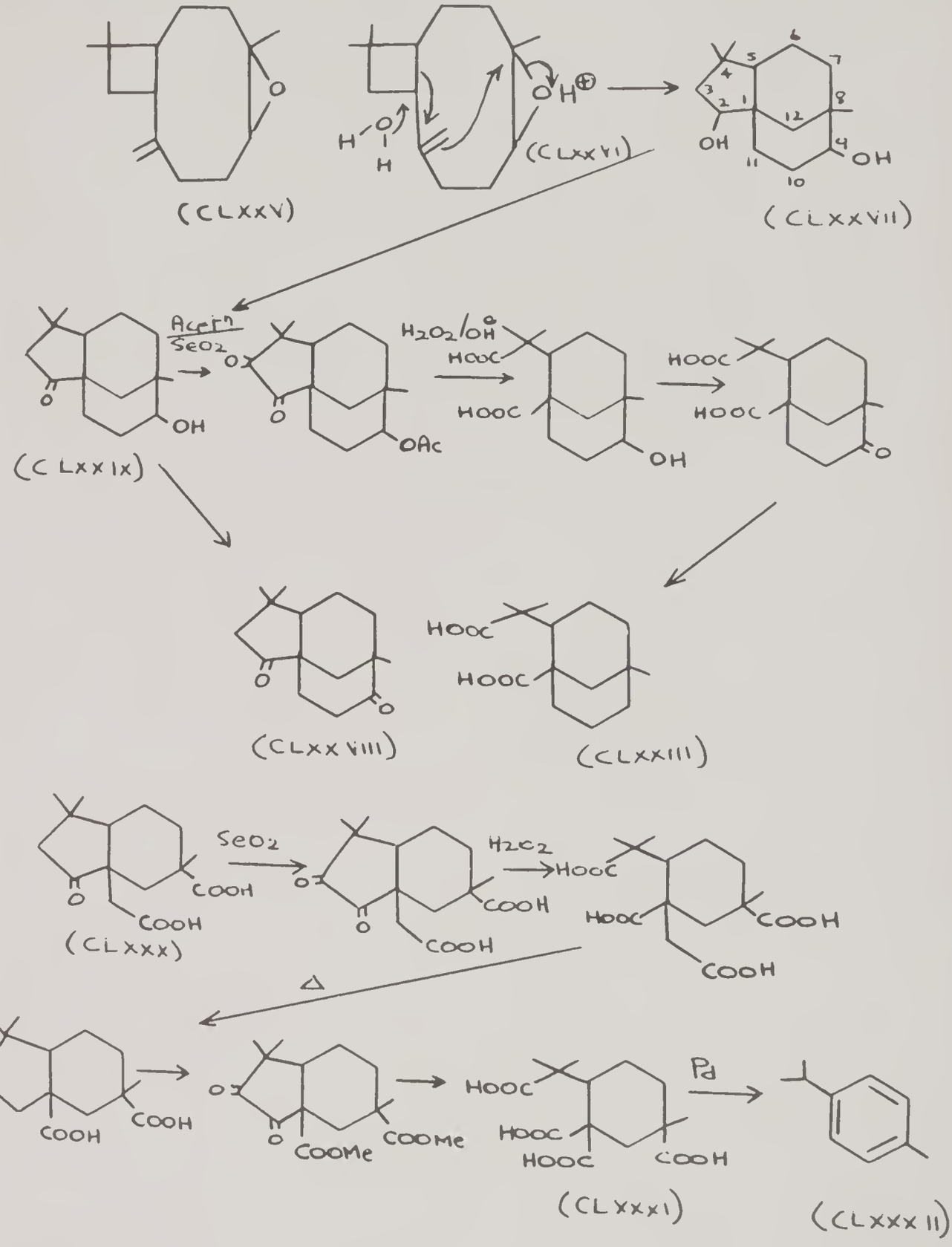
(CLXXI)



(CLXXIV) (CLXXII) (CLXXIII)

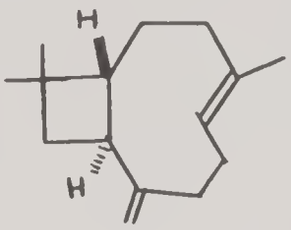
The structure of clovenic acid was rigidly established by Barton and his collaborators. Acid treatment of the epoxide (CLXXV) resulted, as shown in (CLXXVI), in the formation of a diol (CLXXVII), degraded stepwise to clovenic acid. The diketone (CLXXVIII) had bands corresponding to carbonyl groups in a six- and five-membered ring.

From this series of reactions proof of the geometrical isomerism of caryophyllene and *iso*caryophyllene was also derived. *Iso*caryophyllene with monoperphthalic acid gave an epoxide isomeric with (CLXXV) cyclised to an isomer of the diol (CLXXVII) and oxidised to an isomer of the ketol (CLXXIX). Further oxidation, however, gave (CLXXVIII) and so the diols differ only in the configuration of the hydroxyl group at C_9. Since this alcohol is that produced in the opening of the epoxide it follows that the configuration of this, and therefore of the double bond, is the only difference between caryophyllene and *iso*caryophyllene. The proof of structure of clovenic acid was completed (58) by degradation, stepwise, of the diketone clovan-2:9-dione (CLXXVIII). On chromic acid oxidation the ketodicarboxylic acid (CLXXX) was obtained. The subsequent steps led, finally, to the acid (CLXXXI) which was dehydrogenated by palladised charcoal to *p*-cymene (CLXXXII).

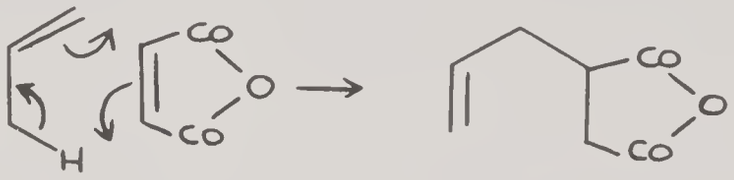

(CLXXV)
(CLXXVI)
(CLXXVII)
Acetn
SeO2
OAc
OH
(CLXXIX)
H2O2/OH
HOOC
(CLXXVIII)
(CLXXIII)
SeO2
COOH
(CLXXX)
H2O2
Δ
COOMe
(CLXXXI)
Pd
(CLXXXII)

On the basis of molecular rotations the absolute configuration of caryophyllene has been shown to be (CLXXXIII) (61).

A particularly interesting reaction of caryophyllene is its formation of an adduct with maleic anhydride (60). The adduct is not of the usual Diels-Alder type, but is formed by attachment to an allylic system with migration of the double bond as illustrated in (CLXXXIV). There are a number of examples of such reactions (59) for which a cyclic transition state has been proposed. That with caryophyllene is exceptional in that reaction takes place in boiling benzene (80°), whereas other cases require temperatures in the region of 200°. The increased reactivity has been attributed to the strain of the *endo*cyclic double bond.



(CLXXXIII)



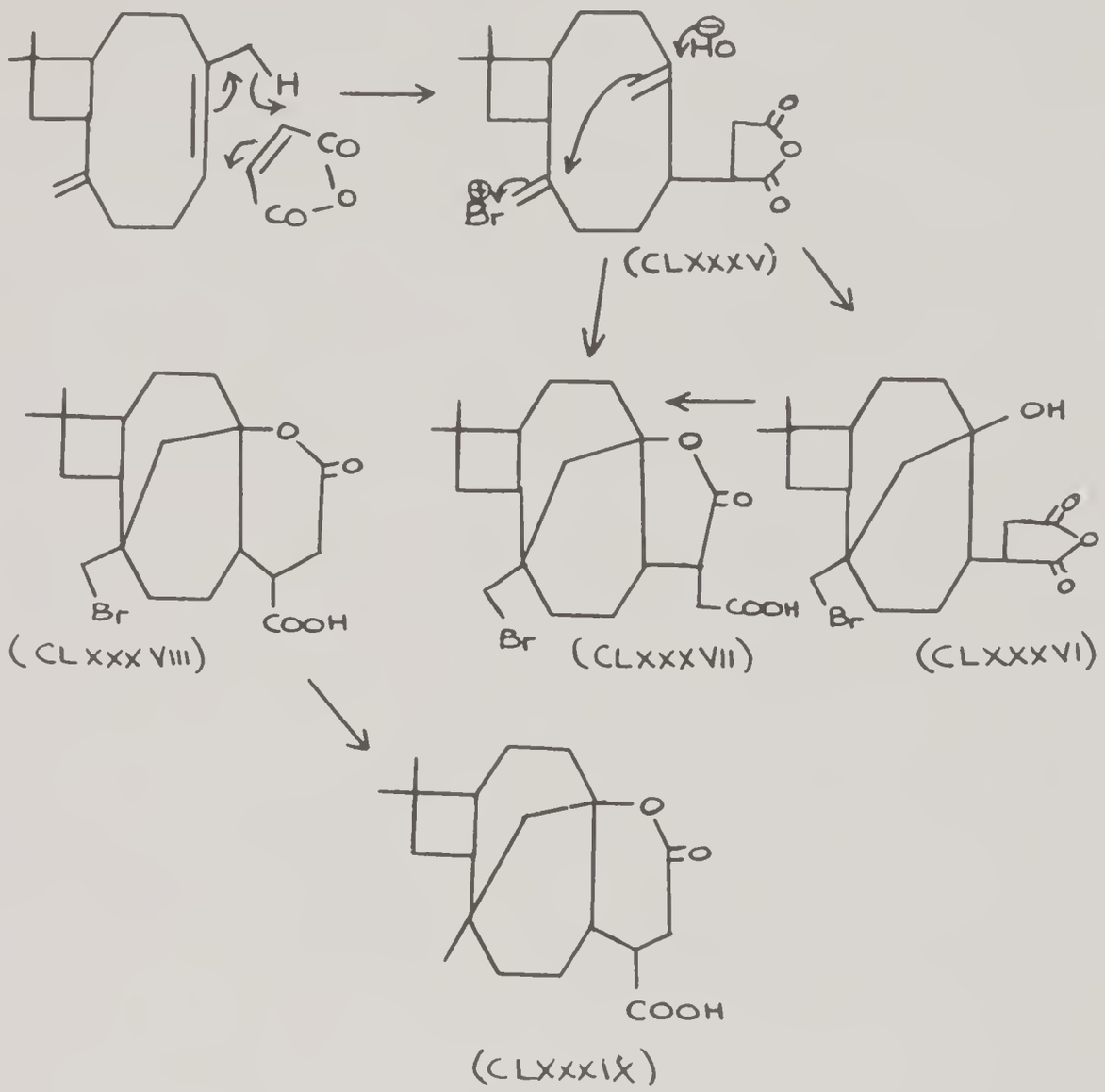
(CLXXXIV)

The caryophyllene adduct (CLXXXV) under the influence of *N*-bromosuccinimide in aqueous dioxan adds the elements of HOBr to give (CLXXXVI) and (CLXXXVII). (CLXXXVI) may be converted into (CLXXXVII) under the mild influence of acid, but under more vigorous conditions both are converted into the δ-lactone (CLXXXVIII) by opening and closing of the lactone ring. Reduction with zinc and acetic acid gave the compound (CLXXXIX) the skeleton of which greatly resembles that of caryolane. The δ-lactone is also obtained by the action of hydrogen chloride on the adduct, followed by acid hydrolysis.

Humulene

Humulene was first isolated from oil of hops in 1895. Some years later it was suggested by Deussen that humulene and the α-caryophyllene from oil of cloves were identical and this was finally confirmed by Sorm and his collaborators (62). More recently the hydrocarbon didymocarpene (from *Didymocarpis pedicellata*) has also been shown to be humulene.

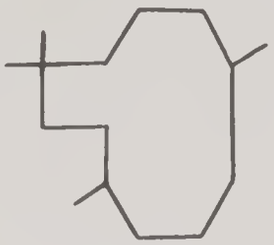
The hydrocarbon has the formula $C_{15}H_{24}$ and since it has been shown to contain three double bonds it is therefore monocyclic. It forms a hexahydro derivative and the Czech workers were able to show that hexahydrohumulene and synthetic 1 : 1 : 4 : 8-tetramethyl-


H
CO
CO
O
HO
Br
O
O
O
(CLXXXV)
O
O
Br
COOH
(CLXXXVIII)
O
O
Br
COOH
(CLXXXVII)
OH
O
O
Br
(CLXXXVI)
O
O
COOH
(CLXXXIX)

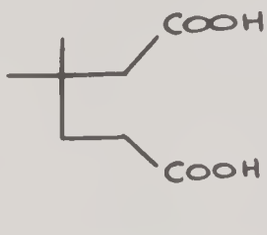
*cyclo*undecane (CXC) were identical, a suggestion that had been previously made by Clemo and Harris (63). The problem was now the disposition of the three double bonds.

Humulene formed a nitrosochloride which gave (64) on hydrogenation a mixture of two bases, α- and β-tetrahydroaminohumulene hydrochloride. After elimination of hydrogen chloride the latter was converted into the quaternary iodide which on Hofmann degradation gave β-dihydrohumulene. Catalytic hydrogenation confirmed the presence of two double bonds in this substance. Potassium permanganate oxidation of β-dihydrohumulene gave *as*-dimethylsuccinic acid, β:β-dimethyladipic acid (CXCI), and a keto acid, $C_{15}H_{24}O_3$ or $C_{15}H_{26}O_3$.

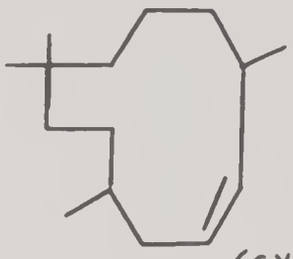
Elimination of hydrogen chloride from α-tetrahydroaminohumulene, with hydrogenation and Hofmann degradation, gave tetrahydrohumulene. Ozonolysis afforded an acid, $C_{15}H_{28}O_4$ (CXCIV or CXCV), and this, it was proposed, must be derived from either (CXCII) or (CXCIII). An acid having one of these formulae was prepared (64) from the anhydride (CXCVI) by the steps shown opposite. This work provided confirmatory evidence of the presence of an eleven-membered ring in humulene. Any formula for humulene must accommodate the above facts, and also that ozonolysis of humulene gives formaldehyde, levulaldehyde, and *as*-dimethylsuccinic acid. The ultraviolet absorption spectrum shows that the double bonds are not conjugated, whilst the Czech workers by a study of the infra-red (band at 975 cm^{-1}) have concluded that the system RCH = CHR is present both in humulene and the nitrosochloride. The structures



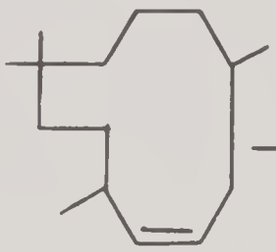
(CXC)



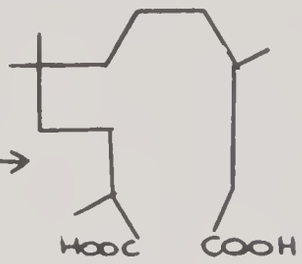
(CXCI)



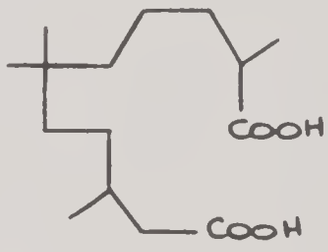
(CXCII)



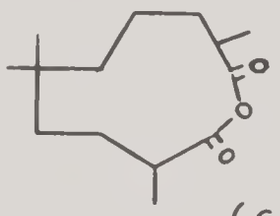
(CXCIII)



(CXCV)



(CXCIV)



(CXCVI)

$$C_{12}H_{24}\begin{bmatrix}-CO\\ \\ -CO\end{bmatrix}O \longrightarrow C_{12}H_{24}\begin{bmatrix}-COOMe\\ -COOH\end{bmatrix} \longrightarrow C_{12}H_{24}\begin{bmatrix}-COOMe\\ -COCl\end{bmatrix}$$

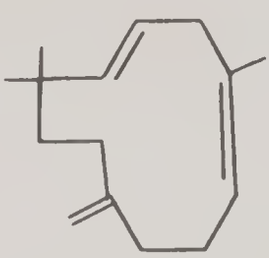
$$\longrightarrow C_{12}H_{24}\begin{bmatrix}-COOMe\\ -COCHN_2\end{bmatrix} \longrightarrow C_{12}H_{24}\begin{bmatrix}-COOMe\\ -CH_2COOMe\end{bmatrix} \longrightarrow \begin{matrix}(CXCIV)\\ or\\ (CXCV)\end{matrix}$$

(CXCVII) and (CXCVIII) have been proposed, but qualification is necessary in both cases. Thus (CXCVII) requires the presence of some (CXCIX), whilst (CXCVIII) requires the assumption that allylic oxidation takes place for the formation of *as*-dimethylsuccinic acid. If humulene is, in fact, homogeneous, then of the above facts the formation of formaldehyde is most suspect.

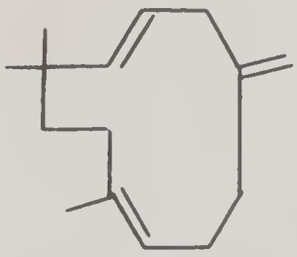
Zerumbone

Zerumbone is a crystalline ketone of the formula $C_{15}H_{22}O$ isolated first by Varier in 1944 from the rhizomes of *Zingiber zerumbet* or wild ginger. It was investigated by Parihar and Dutt (65) who adduced evidence for conjugation of two double bonds present with the carbonyl group, by reduction with sodium and alcohol to give tetrahydrozerumbol oxidised to tetrahydrozerumbone with chromic acid. This has been confirmed by Dev (66) and by Bhattacharyya and his coworkers (72). The former also showed that the alcohol obtained by lithium aluminum hydride reduction was oxidised back to the ketone by activated manganese dioxide. This work leads to the partial formula (CC). On treatment with base (66) zerumbone was cleaved to give methyl ethyl ketone as the only volatile fragment. The formation of this must involve the addition of water (twice) to a conjugated double bond followed by dealdolisation. The partial formula may thus be expanded to (CCI).

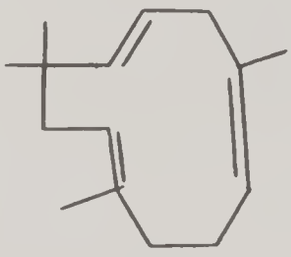
Tetrahydrozerumbone is, however, still unsaturated because hydrogenation in acetic acid with Adams catalyst resulted in the uptake of one molecule of hydrogen and the formation of a mixture of saturated ketones; one pure isomer of hexahydrozerumbone was obtained by repeated crystallisation. Clemmensen reduction of this (66) gave a hydrocarbon which appeared to be identical with humulane. This was biogenetically interesting because humulene has also been stated to occur in this essential oil. Two structures (CCII) and (CCIII) were then probable because the non-conjugated double bond was presumed to be at least triply substituted since isomers were obtained on hydrogenation. Decision between these



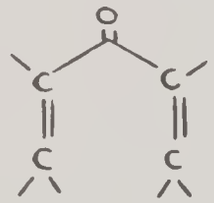
(CXCVII)



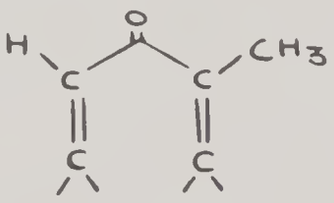
(CXCVIII)



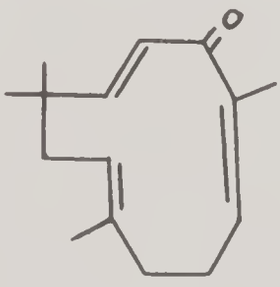
(CXCIX)



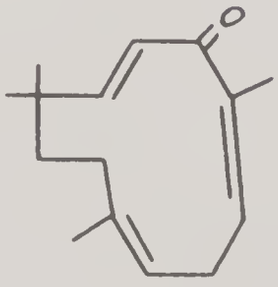
(CC)



(CCI)



(CCII)



(CCIII)

two was possible since ozonolysis of zerumbol (66) gave levulic and *as*-dimethylsuccinic acids obtainable only, as the two main fragments, from (CCII).

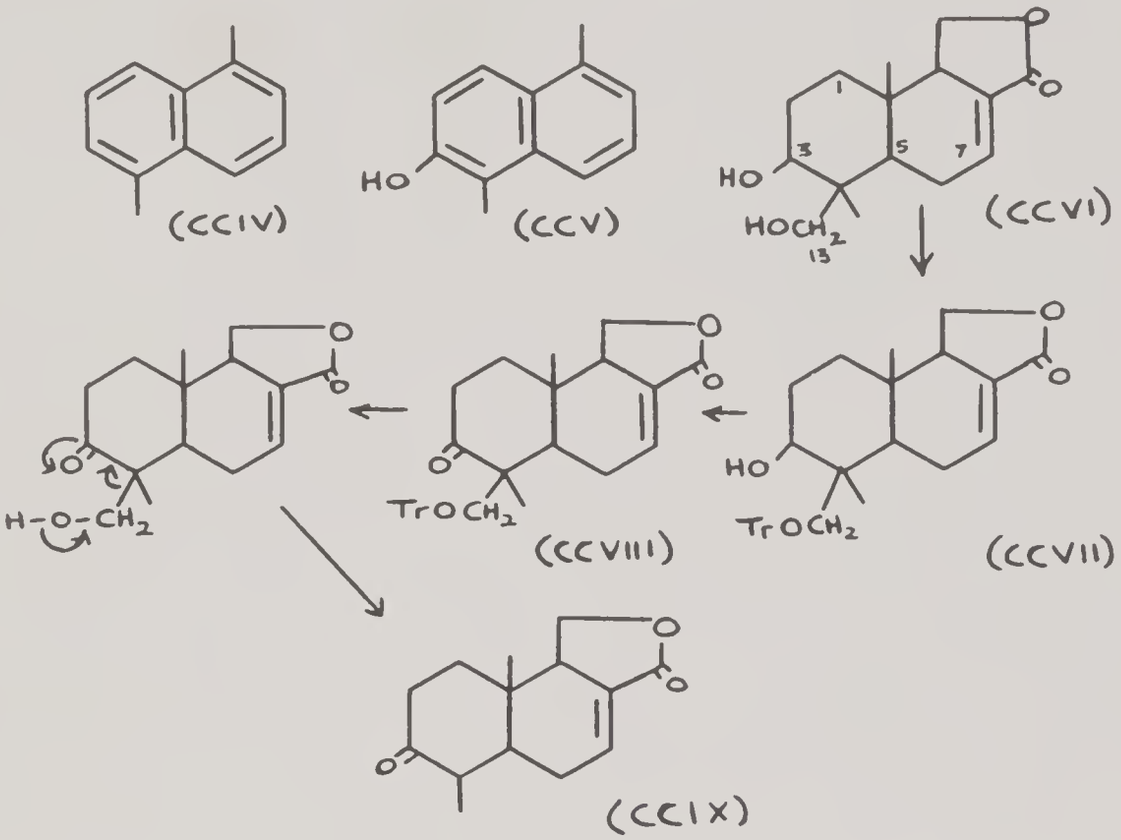
Iresin

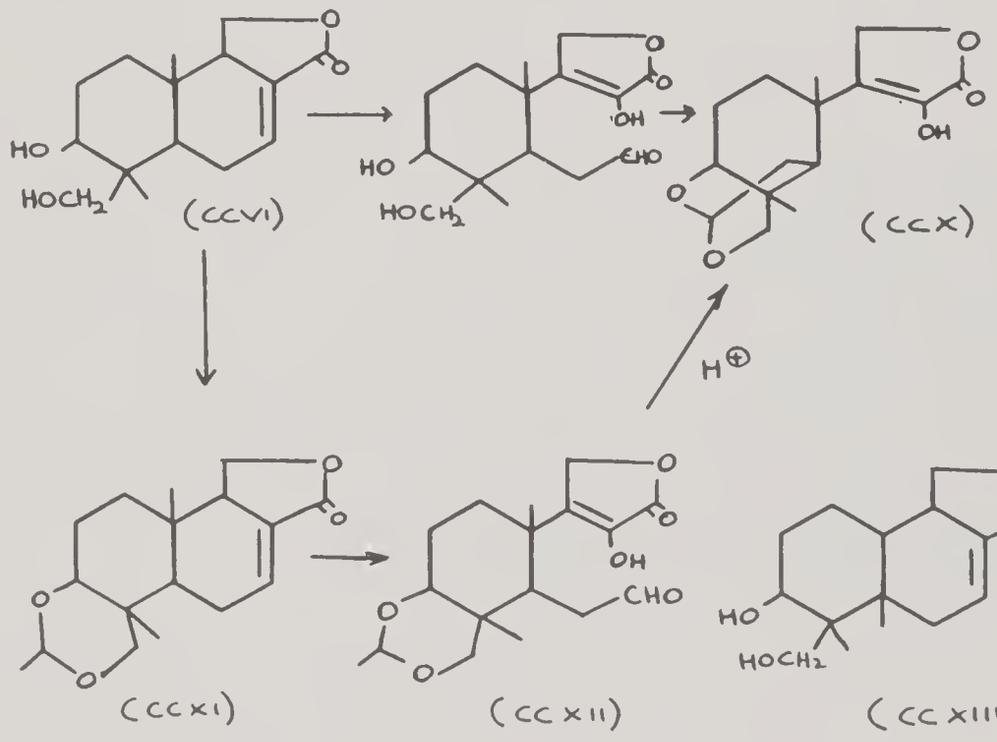
Iresine celosioides is a shrub growing in Mexico, and extracts of it and related species have been used by the natives thereof for the treatment of various diseases even including malaria and typhoid fever. During investigations of this plant Djerassi and his collaborators isolated a sesquiterpenoid lactone, iresin. It had the formula $C_{15}H_{22}O_4$ and, since it gave a diacetate, two of the oxygen atoms were hydroxyl groups; the remaining two were incorporated in a lactone which was, from spectral data, an $\alpha:\beta$-unsaturated γ-lactone (67).

Iresin was presumed to be a 1:3-glycol since it was unaffected by lead tetraacetate, yet nevertheless gave a benzylidene compound. By dehydrogenation with palladium 1:5-dimethylnaphthalene (CCIV) and 1:5-dimethylnaphth-2-ol (CCV) were obtained showing the position of one of the hydroxyl groups. With triphenylmethyl chloride (trityl chloride) a monoether was obtained which on the basis of the formula (CCVI) finally proposed was (CCVII). Oxidation to the ketone (CCVIII) followed by acid hydrolysis resulted in dealdolisation and the loss of formaldehyde to give the norketone (CCIX). This is another example of an elimination like that previously described by Barton and de Mayo in the chemistry of icterogenin. From this it could be deduced that the second hydroxyl group should be placed at C_{13}.

Ozonolysis of iresin cleaved the conjugated double bond to give an α-ketolactone, in the enol form, and a free aldehyde group. The presence of the former grouping was shown by the ultra-violet spectrum in neutral ($\lambda_{max.}$ 240 mμ) and in alkaline ($\lambda_{max.}$ 274 mμ) solution and by conversion to the enol acetate ($\lambda_{max.}$ 218 mμ). The aldehyde formed an internal acetal with the hydroxyl groups to give (CCX). Ozonolysis of acetylidene iresin (CCXI) gave the free aldehyde (CCXII) converted to (CCX) by the action of acid.

On the basis of this and other evidence the structure (CCVI) was


(CCIV)
HO
(CCV)
HO
HOCH2
13
1
3
5
7
(CCVI)
HO
TrOCH2
(CCVII)
TrOCH2
(CCVIII)
H-O-CH2
(CCIX)

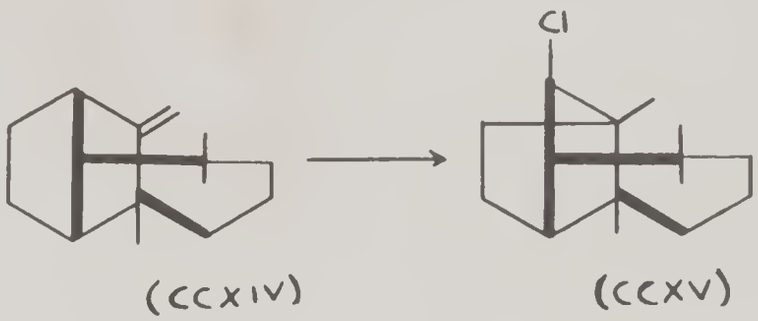

HO
HOCH2
(CCVI)
HO
HOCH2
OH
CHO
(CCX)
OH
H⊕
(CCXI)
OH
CHO
(CCXII)
HO
HOCH2
(CCXIII)

proposed. If correct, it is of considerable biogenetic interest because this bi*cyclo*farnesol system, whilst the rule in the di- and triterpenoids, is not known to occur elsewhere. The authors, however, do not claim to have eliminated the isomeric structure (CCXIII) from consideration.

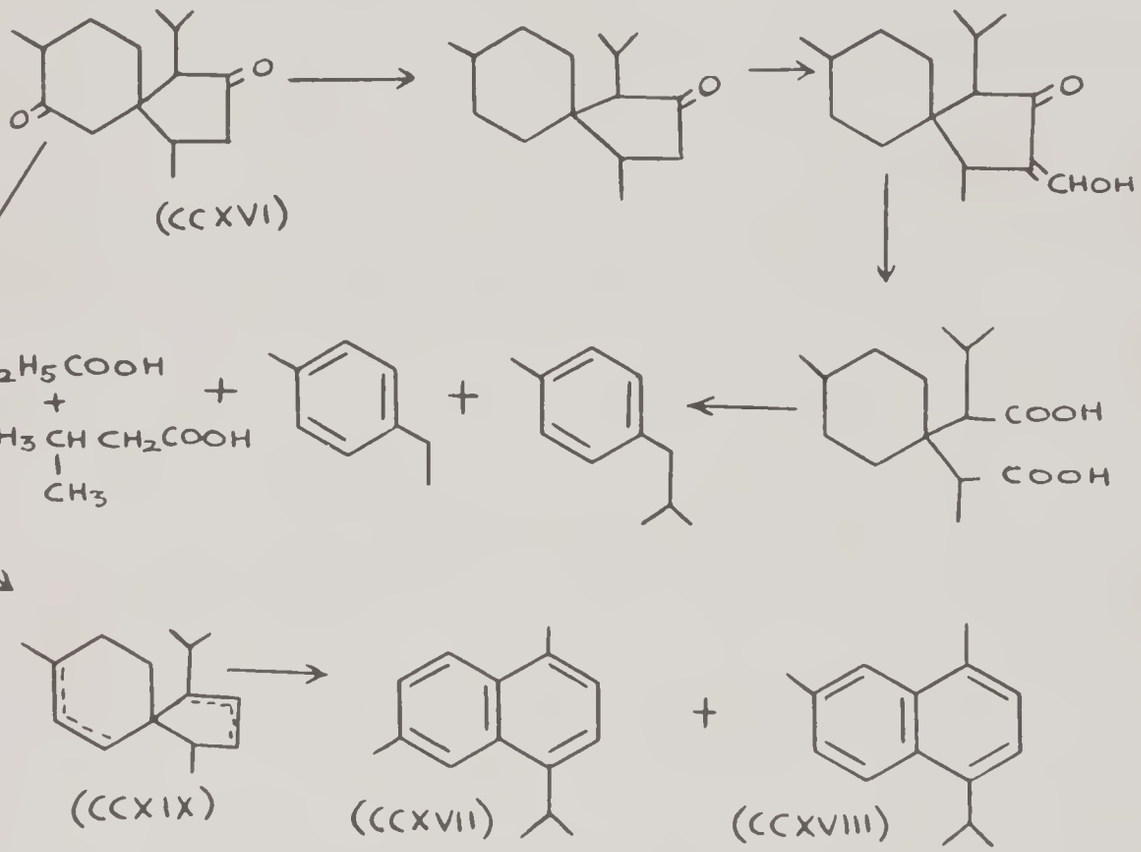
Longifolene is a tricyclic hydrocarbon which occurs in the essential oils from the oleo-resins from *Pinus longifolia, P. maritima*, etc. It was studied in detail by Simonsen (69) and later by a group of French workers (70). Although progress was being made towards the elucidation of its structure, and that of the derived hydrobromide and hydrochloride, the final solution was presented as a result of a brilliant X-ray study by Moffet and Rogers (68) well in advance of chemical work. The change from longifolene (CCXIV) to the hydrochloride (CCXV), which was the subject of the X-ray investigation, is a 1 : 2 shift of the Wagner type familiar in the monoterpenoids. It has been suggested by Ourisson on the basis of molecular rotation considerations that (+)-longifolene was derived from (+)-camphene and hence that (CCXIV) represents the absolute configuration of longifolene.

Acorone

Very recently Sorm and his collaborators have reinvestigated a ketone they isolated in 1948 from sweet flag oil, acorone (71). This substance, some of the evidence for the structure of which is presented below, has been assigned the formula (CCXVI) and is thus the first naturally occurring spirane to be discovered. The spiranic nature is revealed particularly strikingly in the formation of both cadalene (CCXVII) and 1 : 7-dimethyl-4-*iso*propylnaphthalene (CCXVIII) on dehydrogenation of acoradiene (CCXIX). It is possible that an acorone-type intermediate may be involved in the genesis of the alcohol carotol (CCXX), which is a derivative of (CCXVIII). The position of the carbonyl group in the five-membered ring does not appear to have been rigidly established.

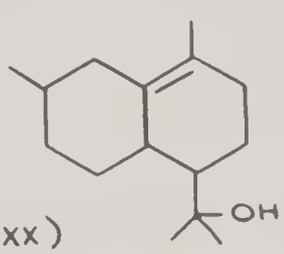


(CCXIV) (CCXV)



(CCXVI)

(CCXIX) (CCXVII) (CCXVIII)



(CCXX)

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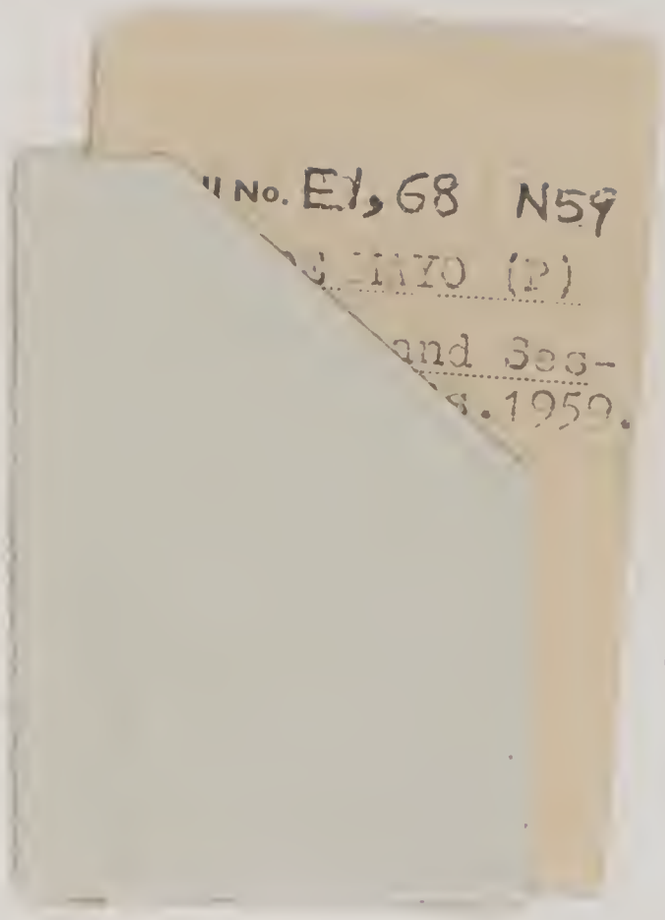
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